STUDIES IN MOLECULAR ASYMMETRY OF BIOLOGICALLY ACTIVE COMPOUNDS

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TO MY FAMILY
WHO BROUGHT ME TO THIS WORLD
AND NOURISHED ME IN IT

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It is a pleasure to thank the many people who contributed in one way or another to my work. I had the good fortune to begin graduate study under the supervision of Dr. John C. Craig; his stimulating teaching drew me into the field of stereochemical studies, and his kindness smoothed the way. Dr. Peter A. Kollman was unfailingly patient and gracious in helping me with problems concerning molecular orbital calculations. I am very grateful to Drs. A. Fredga, A. Paul, S. D. Brown, M. G. Reinecke, L. Marion, H. Beyerman, L. Maat, H. E. Alburn, P. B. Russell, E. Work, and R. E. Moore for the various samples that made the study possible.

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January 1976

ABSTRACT

Chiroptical properties of 1-methyl-1,2,3,4-tetrahydroisoquinolines are reviewed. Previously proposed empirical quadrant and segment rules for these compounds are discussed and some of the difficulties involved in their application pointed out. A semi-empirical quadrant rule based on one-electron theory is developed, which is independent of the substitution pattern in the benzene ring. It is shown to apply correctly to twelve 1-methyl-tetrahydroisoquinolines of known absolute configuration, and is used to assign this in two cases where it is unknown.

The CD spectra of fifteen 2-substituted piperidines and their N-methylated derivatives have been determined. The signs of the Cotton effects observed for the $n \rightarrow \sigma^*$ transition of nitrogen are shown to be correlated, for a given absolute configuration, with the axial or equatorial orientation of the nitrogen lone pair. The screw sense of the helicity between the nitrogen lone pair and the 2-substituent R determines the sign of the Cotton effect: for compounds of the absolute D configuration (=S), a positive helicity gives a positive CD while a negative helicity results in a CD of like sign.

Although the closely related D-(-)-anaferine and D-(-)-pelletierine have the same absolute configuration as shown by oxidative degradation, the sign of the Cotton effect for the carbonyl $n \rightarrow \pi^*$ transition cannot be used for configurational assignment as it is opposite for these two compounds.

The conformation is decisive as evidenced from the sign change for pelletierine base in water and in ethanol. If the carbonyl chromophore is removed, the resulting bases show $n \rightarrow \sigma^*$ transitions with the sign of the Cotton effect in agreement with known model compounds in the α-substituted piperidine series.

The CD spectra of four selenium-containing amino acids were investigated and compared with those of their sulfur and methylene analogues. In the region 190-250 nm, positive Cotton effects of carboxyl and selenide (or sulfide) chromophores always correlate with L(=S) or L,L(=S,S) absolute configurations. The additive nature of such Cotton effects was demonstrated by a "difference curve" method, which permits the chiroptical properties of the Se (or S) chromophore to be determined. Results suggest that the C-Se-C selenide chromophore has three optically active transitions in the near UV range at approximately 225, 210, and 195-200nm. The absolute configuration of natural (+)-selenocystathionine has been established spectroscopically to be L,L (=S,S), in agreement with enzymatic results.

The effect of conformational preference on the chiroptical properties of α-substituted succinic acids and esters has been investigated using variable-temperature CD in solvents of different polarity. All available evidence indicates that when the α-substituent R' is alkyl or halogen, the preferred conformation is different from that when R' is hydroxy, methoxy, or amino. The results when R'=chloro or bromo do not support previously proposed conclusions and an alternative explanation is advanced. In the resultant octant projection it is shown that the sign of the Cotton effect will be determined by the position of the groups in the back octants, and since one of these is always H in the two favored conformations, the sign is actually determined by the position of the other group. This octant projection predicts successfully the sign of the ellipticity of the $n \rightarrow \pi^*$ transition for any α-substituted succinic acid or ester with the appropriate substituent R', and appears to apply also to simple alkanoic acids and esters with the same substituents.

CD spectra of the optically active cyclopropane hydrocarbons Dictyopterene A and Dictyopterene B measured over a range of temperatures, showed these compounds to be configurationally identical. The CD spectrum was found to consist of two overlapping exciton pairs, corresponding to an equilibrium mixture of two solution conformers, for which thermodynamic parameters were calculated. Optical calculations using the exciton model were used to obtain the sign of the rotational strength for the long wavelength part of the exciton pair for different conformers. The result confirmed the absolute (R, R) configuration obtained from oxidative degradation, and the conformational assignment made from spectral analysis showing that the trans-trans conformer is responsible for the pair of exciton bands at shorter wavelength region. Both CNDO/2 and ab initio calculations confirmed that this conformer was of the lowest energy.

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CHAPTER I

CHIROPTICAL PROPERTIES OF 1-METHYL-1,2,3,4-TETRAHYDRO-ISOQUINOLINES: A SEMI-EMPIRICAL QUADRANT RULE BASED ON ONE-ELECTRON THEORY[1]

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ABSTRACT:

Chiroptical properties of 1-methyl-1,2,3,4-tetrahydroisoquinolines are reviewed. Previously proposed empirical quadrant and segment rules for these compounds are discussed and some of the difficulties involved in their application pointed out. A semi-empirical quadrant rule based on one-electron theory is developed, which is independent of the substitution pattern in the benzene ring. It is shown to apply correctly to twelve 1-methyl-tetrahydroisoquinolines of known absolute configuration, and is used to assign this in two cases where it is unknown.

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The 1,2,3,4-tetrahydroisoquinolines comprise an important group of natural products[2] because of their biogenetic relationships to the morphine alkaloids. Many of the simple tetrahydroisoquinolines bear a substituent (usually methyl or benzyl) in the 1-position, and are optically active. Although ORD and CD spectra have been reported[3] for some of these compounds, there is no simple method which allows a correlation of chiroptical properties with their absolute configuration. Several quadrant and segment rules have been proposed,[4-6] utilizing different approaches, but none has, so far, proved to be generally applicable and independent of the substitution pattern in the benzene ring. The reasons for this are briefly discussed, and a semi-empirical rule based on one-electron theory is outlined below.

Ultraviolet Spectra.

Aromatic compounds usually show three major transitions between 180 and 300 nm; two strong absorption bands appear near 180 and 200 nm, and a weak band, usually showing considerable fine structure, appears at about 260 nm. These three transitions are designed ${}^1B_a({}^1A_{1g} \rightarrow {}^1E_{1u})$, ${}^1L_a({}^1A_{1g} \rightarrow {}^1B_{1u})$, and ${}^1L_b$ $({}^1A_{1g} \rightarrow {}^1B_{2u})$, respectively, in the Platt notation.[7] This set of three transitions corresponds to the absorption of energy by excitation of a single electron from the highest occupied π orbital of benzene to the lowest unoccupied π^* orbital. Since the intensity of an electronic transition is proportional to the square of the transition dipole moment vector, for the symmetric benzene itself the intensity of the ${}^1L_b$ transition is zero and is thus said to be "forbidden". Vibrational perturbations cause small distortions in the molecule resulting in a small net transition dipole moment, which accounts for the low intensity actually observed. The ${}^1L_a$ transition is only partially forbidden, and its intensity is therefore about 10 to 100 times higher. The ^1L_a band is also observed to show fine structure. However, the fine structure demonstrated for ^1L_b and ^1L_a transitions in the vapor state or in hexane solution tends to be smoothed out with the use of hydroxylic solvents through solvent-solute interactions. ^1B_a is an electronically "allowed" transition and is of far stronger intensity.

Substitution on the benzene ring results in changes of both the intensities and positions of the absorption bands. The simple tetrahydroisoquinoline alkaloids usually bear oxygen substituents at positions 6 and 7, and occasionally at 5 and 8. This substitution pattern results in a big change of the UV spectrum in comparison with benzene itself. Generally, the ^1L_b transition is shifted to 280 nm (20 nm bathochromic shift), while the ^1L_a transition is moved to 235 nm (35 nm bathochromic shift). Both are accompanied by an increase in the extinction coefficient and loss of fine structure.

Theoretical studies[8,9] showed that such changes of intensity are caused by substitution perturbations so that the two lower energy transitions mix with the allowed ^1B_a transition. The resultant electronic contribution to the intensity is of the same order of magnitude as the vibrationally induced ^1L_b intensity. Therefore, the effect is proportionately much greater for the ^1L_b transition than for the ^1L_a transition. The wavelength shift, however, is considered to arise from two different sources.[8,9] The first order contribution comes from interactions of the lower energy transitions (^1L_a or ^1L_b) with a higher energy "charge-transfer" state of the substituent, i.e., overlap of the π orbital of benzene with the nonbonding p orbital of oxygen, and this effect is larger for ^1L_a than for ^1L_b. The second order contribution again comes from the mixing of the ^1B_a transition with the ^1L_a or ^1L_b transition. In most cases, the net result is that the ^1L_a shift is greater than the ^1L_b shift and this is what is observed here for the 1-methyltetrahydroisoquinoline alkaloids 1. The total UV spectrum corresponds to an o-xylene chromophore [λ_{max} 210 nm(ϵ 8300) and λ_{max} 262.5 nm (ϵ 300)] with the addition of oxygen substituents in the benzene ring (Table I).

CD & ORD Spectra

On symmetry grounds, the ^1L_b transition is considered as a formally forbidden transition. However, if the chromophore is situated in an asymmetric environment, the symmetry element is removed and the transition then becomes optically active. The CD spectra of 1-methyltetrahydroisoquinolines 1 are shown in Table II. CD and ORD measurements on compounds with such an asymmetrically perturbed aromatic chromophore have led to the proposal of several empirical rules correlating Cotton effects with their absolute configurations. Kuriyama et al.[4] put forward a quadrant rule for the chiral ^1L_b transition. The benzene chromophore is pictured along its C_2-axis of symmetry and the contribution of the group in each quadrant to the sign of the 290 nm Cotton effect is shown in Fig. 1. However, it is clear that this rule applies only to those compounds symmetrically substituted at the 6 and 7 positions, i.e. those possessing C_2 symmetry. Kuriyama's rule therefore cannot be applied to compounds substituted at positions other than 6 and 7. De Angelis and Wildman[5] also proposed a quadrant rule. It is for the ^1L_a transition and the compound under consideration has to have an asymmetric center adjacent to the aromatic ring (Fig. 2) with the signs of the quadrants as shown.

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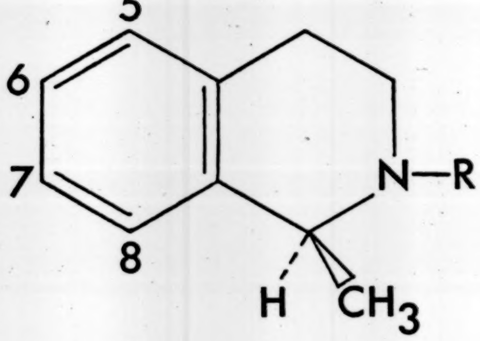

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Table I. UV Spectra of 1-Methyl-1,2,3,4-tetrahydroisoquinolines

Compound No.	Name	Substition					λ_{max}(nm); (log			
		R	5	6	7	8				
1·HCl	1-Methyl-1,2,3,4-tetrahydroisoquinoline	H					208 (3.97)	251* (2.47)	256* (2.57)	26 (2.
2·HCl	1,2-Dimethyl-1,2,3,4-tetrahydroisoquinoline	Me					208 (3.98)	251* (2.25)	256* (2.38)	26 (2.4
3	Salsoline	H		OH	OMe		202 (4.94)	225 (4.25)	235* (4.02)	28 (3.
4·HCl	N-methyl salsoline	Me		OH	OMe		208 (4.59)	227 (3.85)	235* (3.74)	28 (3.
5	Salsolidine	H		OMe	OMe		204 (4.57)	225 (3.85)	232* (3.82)	27 (3.
6·HCl	Carnegine	Me		OMe	OMe		203 (4.67)	224 (3.96)	232* (3.90)	27 (3.
7	O-Methyl Anhalonidine[10]	H		OMe	OMe	OMe	207 (4.61)	228* (3.97)	273 (3.09)	28 (3.
8	Gigantine[33]	Me	OH	OMe	OMe		205 (4.8)			
10·HCl	Anhalonine[10]	H		OMe	$-OCH_2O-$		214 (4.67)	250* (3.43)	277 (2.99)	28 (2.
11·HBr	Lophophorine[10]	Me		OMe	$-OCH_2O-$		211 (4.63)	250* (3.47)	278 (3.03)	28 (3.
12·HCl	Anhalonidine[35]	M		OMe	OMe	OH	230* (3.92)	271 (2.90)	280* (2.78)	
13·HCl	Pellotine[34]	Me		OMe	OMe	OH	230* (3.99)	271 (2.96)	281* (2.85)	
14·HCl	1,2-Dimethyl-7-methoxy-1,2,3,4-tetrahydroisoquinoline[42]	Me			OMe		199 (3.61)	227 (2.88)	279 (2.31)	287 (2.2

*shoulder

ctra of 1-Methyl-1,2,3,4-tetrahydroisoquinolines in 95% Ethanol.

Substition				λ_{max}(nm); (log ε)						
5	6	7	8							
				208 (3.97)	251* (2.47)	256* (2.57)	264 (2.66)	267* (2.60)	271 (2.65)	285* (2.23)
				208 (3.98)	251* (2.25)	256* (2.38)	264 (2.48)	267* (2.39)	271 (2.44)	
	OH	OMe		202 (4.94)	225 (4.25)	235* (4.02)	283 (3.84)			
	OH	OMe		208 (4.59)	227 (3.85)	235* (3.74)	280 (3.35)	285 (3.36)		
	OMe	OMe		204 (4.57)	225 (3.85)	232* (3.82)	277* (3.44)	282 (3.53)	287 (3.53)	292* (3.44)
	OMe	OMe		203 (4.67)	224 (3.96)	232* (3.90)	275* (3.47)	282 (3.59)	286 (3.59)	291* (3.51)
	OMe	OMe	OMe	207 (4.61)	228* (3.97)	273 (3.09)	280 (3.11)			
OH	OMe	OMe		205 (4.8)						
	OMe	$-OCH_2O-$		214 (4.67)	250* (3.43)	277 (2.99)	286* (2.94)			
	OMe	$-OCH_2O-$		211 (4.63)	250* (3.47)	278 (3.03)	286* (3.98)			
	OMe	OMe	OH	230* (3.92)	271 (2.90)	280* (2.78)				
	OMe	OMe	OH	230* (3.99)	271 (2.96)	281* (2.85)				
		OMe		199 (3.61)	227 (2.88)	279 (2.31)	287 (2.28)			

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Table II. CD Spectra of 1-Methyl-1,2,3,4-tetrahydroisoquinolines i

Compound	Name	Substitution						1_{L}
No.		R	5	6	7	8	$[\alpha]_D^a$	$[\theta]_{ma}$
1	1-Methyl-1,2,3,4-tetrahydroisoquinoline[42]	H					-66.2°[c]	+800
1· HCl								+360
2	1,2-Dimethyl-1,2,3,4-tetrahydroisoquinoline[42]	Me					-51°	+1000
2·HCl							-0.17°	+320
2·MeI							-2.7°	+190
3	Salsoline[b]	H		OH	OMe			+1910
3·HCl							-27°[d]	+1800
4	N-Methyl Salsoline	Me		OH	OMe		-33.5	+1560
4·HCl							+9.7°	+1250
4·MeI							+10.3°	+1400
5							-60°[e]	+1970
5·HCl	Salsolidine	H		OMe	OMe		-24°[f]	+1850
6	Carnegine	Me		OMe	OMe		-25°[g]	+2630
6·HCl							+6°	+2210
6·MeI							+9.8°	+2520
7	Gigantine	Me	OH	OMe	OMe		+28.7°[j]	-310
7·HCl							+8°	+210
8	O-Methyl Anhalonidine	H		OMe	OMe	OMe	+24[i]	+130
8·HCl							+34.6°	+170

of 1-Methyl-1,2,3,4-tetrahydroisoquinolines in 95% Ethanol.

stitution						^1L_b Band	^1L_a Band
	5	6	7	8	$[\alpha]_D^a$	$[\theta]_{max}$ (nm)	$[\theta]_{max}$ (nm)
					-66.2°[c]	+800 (273)	-2100 (221)
						+360 (272)	-1620 (219)
					-51°	+1000 (273)	-9290 (220)
e					-0.17°	+320 (272)	-3180 (217)
					-2.7°	+190 (269)	
		OH	OMe			+1910 (283)	+4210 (225), +3650 (235)
					-27°[d]	+1800 (282)	+7020 (217), +5050 (235)
e		OH	OMe		-33.5	+1560 (280)	+2070 (220), +4150 (233)
					+9.7°	+1250 (282)	+5190 (213), +6220 (235)
					+10.3°	+1400 (286)	+6090 (219), +10970 (235)
					-60°[e]	+1970 (281)	+3990(220), +3990 (237)
		OMe	OMe		-24°[f]	+1850 (279)	+6300(215), +7760 (235)
e		OMe	OMe		-25°[g]	+2630 (280)	+8500 (200),+5100 (232)
					+6°	+2210 (280)	+8500 (212), +13,600 (234)
					+9.8°	+2520 (280)	+6000 (212), +13,180(235)
e	OH	OMe	OMe		+28.7°[j]	-310 (276)	+870 (240)
					+8°	+210 (283)	+120 (245)
		OMe	OMe	OMe	+24[i]	+130 (280)	+2930 (233)
					+34.6°	+170 (285)	+11,280 (233)

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9	O-Methyl Pellotine	Me	OMe	OMe	OMe	+16°	+310
9·HCl							+80
10	Anhalonine	H	OMe	$-OCH_2O-$		-52°[k]	-340 +110
10.HCl							-640
11	Lophophorine	Me	OMe	$-OCH_2O-$		-34.7°[l]	-450 + 50
11·HCl						-18°[m]	-920
12	Anhalonidine (natural)[32]	H	OMe	OMe	OH	-21.2°[n]	-330
12·HCl						-0.7°[n]	-134
13	Pellotine (natural)[32]	Me	OMe	OMe	OH	-1.1°[n]	
13·HCl						-0.7°[n]	
13	Pellotine (from natural anhalonidine)[32]	Me	OMe	OMe	OH	-11.1°[n]	-1020
13·HCl						-7.8°[n]	-1020
14	1,2-Dimethyl-7-methoxy-1,2,3,4-tetrahydroisoquinoline[42]	Me		OMe		-7.2°	+510 +500 -185
14·HCl						-3.0°	+510 -230

[a] Rotations were measured in 95% ethanol (c 0.1 - 1.0) unless otherwise indicated. S-configuration.

[b] Natural R-(+)-salsoline was used; the (-)-enantiomer is reported here for consisten

[c] Lit[36] - 71.5° [d] measured in H_2O Lit[37] + 40° (H_2O) for the R-(+)-compound.

[e] Lit[37] - 63°. [f] Lit[38] - 23.4° [g] Lit[38] - 25° [h] Lit[38] + 6.6° [i] Measured

[k] Lit[41] - 56.3° ($CHCl_3$) [l] Lit[41] - 47.3° ($CHCl_3$ [m] Lit[41] - 16.3° (H_2O).

OMe	OMe	OMe	+16°	+310 (277)	+930 (233), -100 (246)
				+80 (284)	+4140 (235), -190 (267)
OMe	$-OCH_2O-$		-52°[k]	-340 (275) +110 (290)	-4910 (221) +2240 (240)
				-640 (275)	+3540 (240)
OMe	$-OCH_2O-$		-34.7°[l]	-450 (277) + 50 (290)	-5860 (220), +3800 (245)
			-18°[m]	-920 (282)	+6430 (242.5)
OMe	OMe	OH	-21.2°[n]	-330 (289)	+9810 (225), -3680 (253)
			-0.7°[n]	-1340 (278)	+2100 (235)
OMe	OMe	OH	-1.1°[n] -0.7°[n]		
			-11.1°[n]	-1020 (277)	-1825 (235!)
OMe	OMe	OH	-7.8°[n]	-1020 (277)	-1300 (235!)
	OMe		-7.2°	+510 (271) +500 (277) -185 (290)	-415 (230!)
			-3.0°	+510 (275) -230 (289)	-740 (232!)

c 0.1 - 1.0) unless otherwise indicated. All compounds except 12 and 13 have the

-enantiomer is reported here for consistency.

+ 40° (H_2O) for the R-(+)-compound.

t [38] - 25° [h] Lit[38] + 6.6° [i] Measured in MeOH. Lit[39] + 20.5° [j] Lit[40] +27.1°($CHCl_3$)

$CHCl_3$ [m] Lit[41] - 16.3° (H_2O).

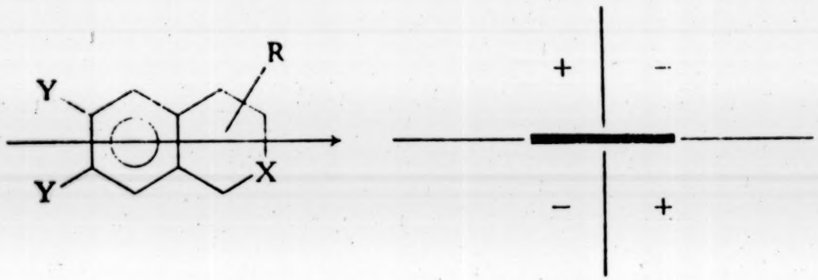

Fig. 1. Quadrant Rule of Kuriyama et al.[4] for ^1L_b Band CD.

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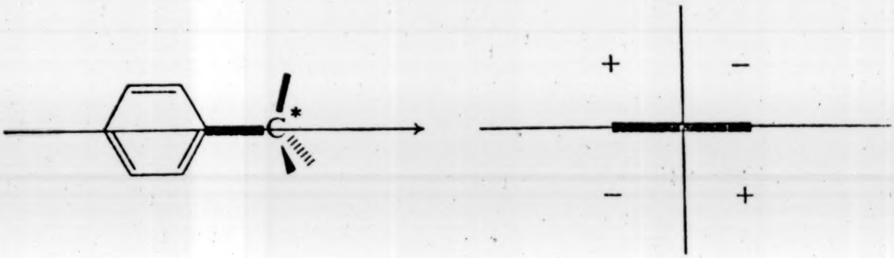

Fig. 2. Quadrant Rule of De Angelis and Wildman[5] for ^1L_b Band CD.

In the case of S-(+)-O-methyl anhalonidine·HBr (8·HBr), both the absolute configuration and conformation are known from X-ray data.[10] When the rule of De Angelis and Wildman is applied to this compound (8a), it predicts a negative Cotton effect for the $^{1}L_{a}$ band, whereas the experimentally observed Cotton effect is positive from the CD spectrum (Table II). Similar discrepancies also occur in the case of other compounds, e.g. 3, 4, 5, 6, etc.

Snatzke et al.[6] took a somewhat different approach: they rationalize the experimental results for the $^{1}L_{b}$ band by taking into account both the effect of the substitution pattern of the benzene ring and chiral contributions from the second and third spheres.[6] For a tetrahydroisoquinoline, the aromatic ring forms the first sphere (achiral), the piperideine ring the second, and groups or rings attached to this second sphere comprise the third sphere. The piperideine ring can assume two conformations referred to[6] respectively as P-helicity 15a and M-helicity 15b. When the benzene ring is not further substituted, P-helicity gives rise to a positive, and M-helicity to a negative sign of the $^{1}L_{b}$ CD band.[6] To determine the influence of the substituents in the benzene ring on the CD sign, spectroscopic moments[11] are used in this treatment as illustrated in Fig. 3. This shows the relationship[12] between the direction of the sum of the spectroscopic moments and the sign of the sectors for third sphere contributions, together with the sign of the second sphere contribution for P-helicity.

As both the absolute configuration and conformation of S-(-)-anhalonine·HBr (10·HBr) have been established by X-ray crystallography[10] a test of Snatzke's rule is possible on the basis of actual experimental data. Compound 10·HBr is a 6-methoxy-7,8-methylenedioxy-substituted tetrahydroisoquinoline. As shown in Fig. 3, since the second sphere of 10·HBr adopts an M-helicity

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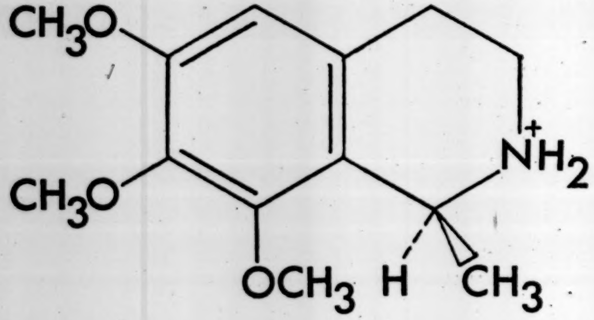
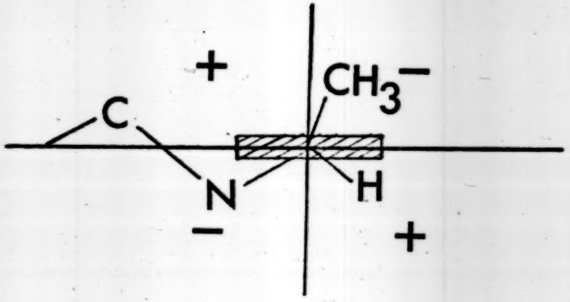


8.HBr



8a

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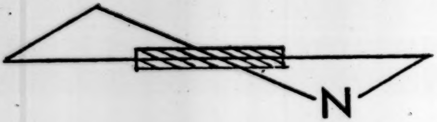
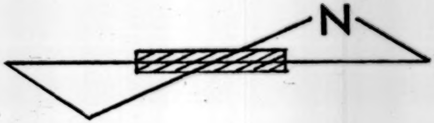


15a



15b

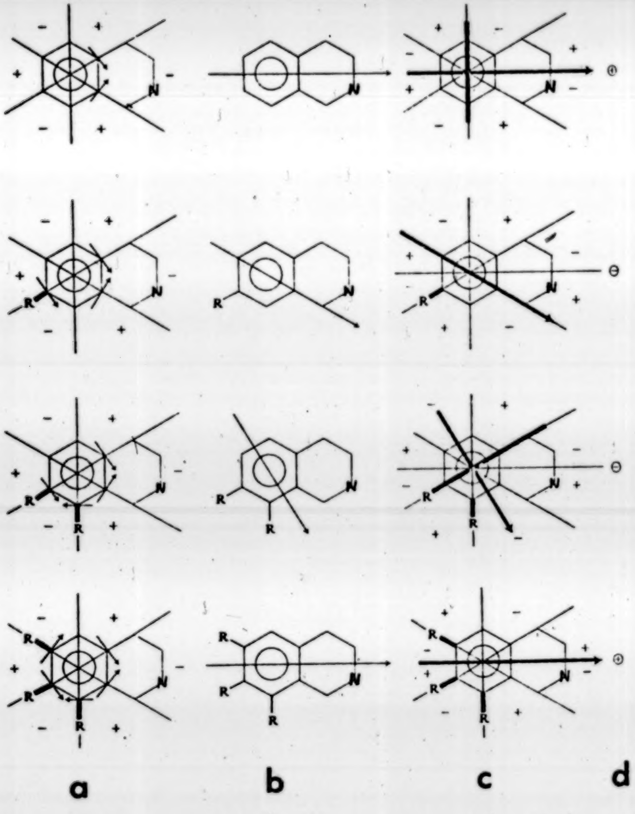


Fig. 3. Effect of Substitution Pattern on Sign of ^1L_b Band CD of tetrahydroisoquinolines[6]

a: Platt Polarization Diagrams
b: Direction of Sum Vector of Spectroscopic Moments
c: Sector Rules for Third Sphere Contributions
d: Sign of CD for Second Sphere Contributions for P-helicity of Piperideine Ring

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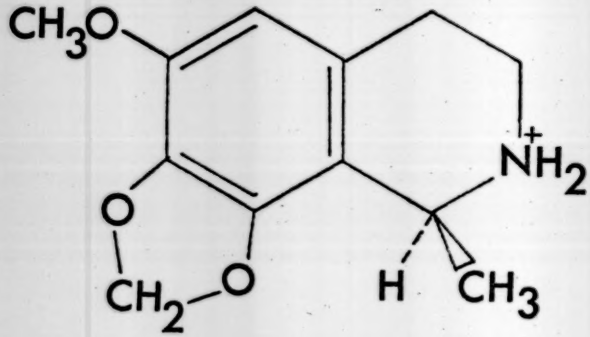
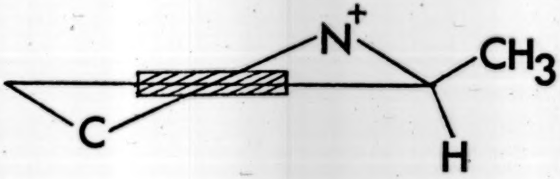


10.HBr



10a

(10a), it should lead to a negative CD for the ^1L_b band. The third sphere contribution, however, leads to a positive CD for that band. The net result thus depends upon the relative importance of these two opposite contributions. As in the case of the analogous tetrahydropalmatine,[13] the prediction of sign of the ^1L_b CD band is complicated because of the presence of two oppositely-signed rotational contributors in the molecule, and without knowing the experimental result, it is impossible to make an unambiguous assignment. In fact, the experimental result shows 10·HBr to have a negatively-signed ^1L_b CD band (Table II). There appears therefore to be no consistent basis for assigning the relative importance of the spheres when they have oppositely signed contributions, to determine the sign of the resultant CD where it is unknown, and although the approach of Snatzke et al. is an interesting one, it does not as yet permit an unequivocal assignment of the sign of the Cotton effect in such cases. What is required is a simple rule which would permit unequivocal sign assignment of tetrahydroisoquinolines independent of the substitution pattern in the benzene ring if the conformation is known. Such an approach is described below.

Theoretical Background

Optically active chromophores can generally be assumed to belong to one of the two limiting forms:[14-16] (i) inherently dissymmetric chromophores, or (ii) asymmetrically perturbed symmetric chromophores. However, as electron exchange between a chromophore and its surroundings becomes appreciable, the chromophoric system is accordingly enlarged. Thus, the latter limiting case smoothly passes over to the former through charge transfer and appreciable overlap between chromophore and environment. Examples of inherently dissymetric chromophores are hexahelicene and certain other conjugated double bond systems.[17] For the asymmetrically perturbed symmetric chromophores, two theories evolved at an early date, the coupled oscillator[18] and the one-electron[19] theories. In the coupled oscillator, or polarizability, theory the individual electric transition moments of different groups of the molecule are coupled by dipole-dipole interactions. For effective coupling one requires either large transition moments (strong absorption bands) or virtual contiguity of the two groups. Therefore, the Cotton effects of strong absorption bands are conventionally treated by this theory. The one-electron theory, on the other hand, proposes a model for optical rotation to arise from the static asymmetric perturbing field of the rest of the molecule (atoms other than the chromophore itself) and not from a reciprocal coupling mechanism. The application of this model is best known for its successful treatment of the optically active ketone transition, thus providing the best accepted theoretical basis for the ketone octant rule.[20]

As mentioned above, the aromatic ^1L_b transition is a weak transition and the application of the coupled-oscillator theory is thus not suitable in the present case. Condon, Altar and Eyring, in their original work, made an attempt to calculate the rotatory power of the phenyl band in methyl phenyl carbinol nitrite.[19] This provides the first example applying the one-electron theory to the aromatic chromophore. The good agreement obtained between theory and experiment[19] prompted us to use a similar approach in exploring the Cotton effect of the ^1L_b transition of the 1-substituted tetrahydroisoquinoline alkaloids which (like methyl phenyl carbinol nitrite) have an asymmetric center adjacent to the benzene ring.

One-Electron Theory

Following the successful treatment of atomic spectra principally from one-electron transitions, the same procedure is usually adopted in interpreting most molecular spectra. Optical activity, being a phenomenon closely related to electronic transitions, may therefore be treated in the same way, i.e. using the one-electron theory of optical activity. The main features in this theory are that an electronic transition occurs in a fairly well-localized group in the molecule (the chromophoric group) and the electron which makes a transition is moving in a force field principally due to the immediate atoms to which it belongs and secondarily due to the fields set up by the effective charge distributions of the other atoms in the molecule. It is this secondary force field due to perturbation by the neighboring atoms which is responsible for the optical activity. The simplest model for discussion would be an anisotropic oscillator assuming an electron moves in a dissymmetric potential field in which the potential energy as a function of Cartesian coordinates X, Y, and Z is given by eq. (1).

$$V = 1/2\ k_1 X^2 + 1/2\ k_2 Y^2 + 1/2\ k_3 Z^2 + AXYZ \qquad \text{eq. (1)}$$

This is the equation of a twisted polarization ellipsoid.[19]

The term in A is what produces the necessary dissymmetry. It is directly proportional to rotational strength and has sign and value defined as in eq. (2).

$$A = \frac{5}{2} e \sum_s e_s \frac{X_s Y_s Z_s}{R_s^7} \qquad \text{eq. (2)}$$

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(X_s, Y_s, Z_s) is the position of a perturbing atom, s, with point charge e_s located at the center of each atom and $R_s = \sqrt{X_s^2 + Y_s^2 + Z_s^2}$. Following the detailed discussion in ref. 19, it is clear that the most important effects of the vicinal perturbers are the removal of the axes of symmetry and of the planes of symmetry possessed by the unperturbed polarization ellipsoid. For formal calculations, one has to know the angle of twist of the principal axes of this ellipse. In comparison to other chromophores, the π electrons of benzene are actually much more stiffly bound in the direction at right angles to the ring than in the other two directions, and will offer a certain amount of resistance to the tilting of its principal axes by the vicinal perturbers. The resultant tilting (while still of importance in causing the optical activity) is therefore small enough to be ignored for an approximate calculation of A by eq. (2). Therefore one can take the three axes as they are in the unperturbed state and reduce the problem to the determination of A directly. (The same approximation has been used in all previously discussed empirical rules[4-6], although this has not been explicitly stated.) Since the magnitude of vicinal interactions between atoms due to point charges is always small and falls off rapidly with increasing distance, it is clear that only first-order, i.e. coulombic, contributions to optical rotation are important. Atoms more than two bonds away from the asymmetric center may therefore be neglected in the calculation of A without affecting its qualitative picture. A right handed coordinate system is set up with the origin at the center of the benzene ring (Fig. 4). Vicinal charges on every atom involved, i.e. adjacent to the asymmetric center, may be calculated in such a way as to represent the observed values of the static dipole moments arising from each bond. The so called "bond charge" has been defined[21] as a quantity which when multiplied by bond length

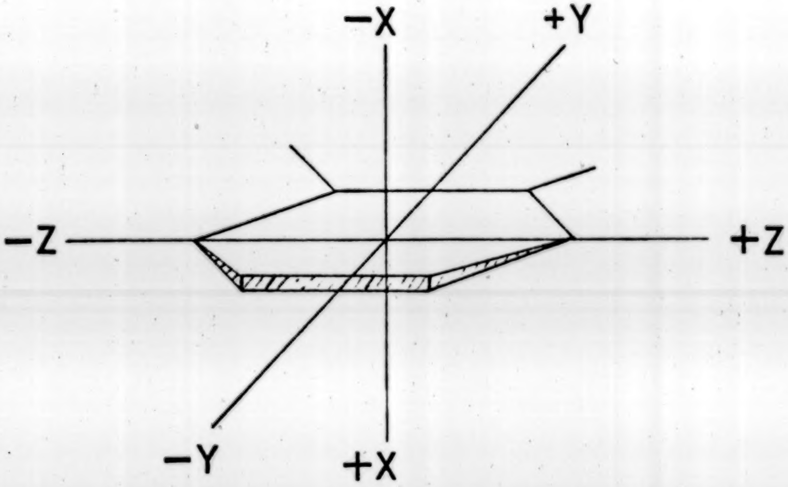

Fig. 4. Coordinate System for Calculation of Sign of ^1L_b CD Band

gives the value of bond moment, and summation of all the bond charges relating to one atom gives the point charge on that atom. Once the coordinates and point charges are known, A can be determined easily according to eq. (2).

For all the simple tetrahydroisoquinoline alkaloids studied, the chiral moiety (piperideine ring) always falls in the octants composed of +Y coordinates of Fig. 4. From a molecular model, the piperideine ring may assume two conformations 16a and 16b with an opposite sense of helicity relative to the benzene ring. When these two conformations are projected in the coordinate system provided, C(1) and C(4) are in the YZ plane, therefore they do not contribute to the optical activity in either case. The exclusion of possible contributions from C(1) and C(4) simplifies the calculation to a great extent, yet the remaining computation, especially the portion which concerns the calculation of $\frac{XYZ}{R^7}$ for every atom, is still very time consuming. However, if it is only desired to obtain the sign of A in order to assign the absolute configuration or conformation of a compound, eq. (2) may be simplified for this purpose with two assumptions:

(i) atoms two bonds away from the asymmetric center are of negligible significance in causing the optical activity, and may therefore be neglected from consideration.

(ii) If a formal charge, +e, is put on the N atom as in the salt or quaternary salt, $\frac{X_s Y_s Z_s}{R_s^7}$ may be assumed to be of about the same magnitude for every atom under consideration. This numerical factor can then be taken out of the summation sign and eq. (2) is reduced to eq. (3):

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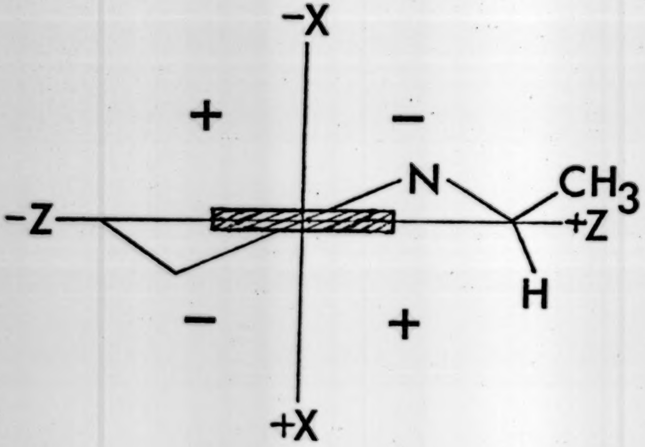
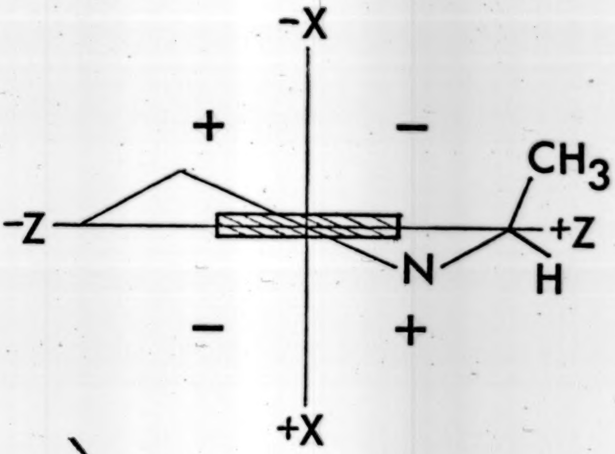


16b



16a

$$A \simeq \frac{5}{2} e \frac{XYZ}{R^7} \sum_s e_s x_s^i y_s^i z_s^i \qquad \text{eq. (3)}$$

where x^i, y^i and z^i are unit coordinates with value ± 1 (see Table V). From the available data on bond moment[22] and bond length (Table III), the point charge on every atom can be calculated (Table IV). As indicated in Table IV, the substitution pattern of the N atom has a definite effect on the charge distribution. Combining these point charge data and coordinate dispositions of **16a** and **16b**, the sign of the ^1L_b CD band can now be found by simple manipulation of $\sum_s e_s x_s^i y_s^i z_s^i$ (Table V). The results show that with similar charge distribution around the asymmetric center, the opposite sense of helicity of the heterocyclic ring from the plane of the benzene ring thus leads to the opposite sign of the ^1L_b CD band.

It is known from X-ray data[10] that **8**·HBr has the P-conformation **16a** in the solid state. According to the prediction (Table V), this compound should have a positive CD for the ^1L_b band. This is exactly what is observed in CD measurements (Table II). When adopting the P- conformation, the 1-methyl group is in the pseudo-axial position which, with the presence of 1,3-diaxial steric interactions, would generally be less favored than the pseudo-equatorial one. However, there are two other factors that would counterbalance this situation: (i) the steric interaction between a C(8) -O-methyl and a C(1)-methyl group is considerably greater, (ii) in occupying the pseudo-axial position, the C(1)-methyl leaves the charged N more accessible for the expected solvation from the polar solvent used (95% EtOH) than it would be in the pseudo-equatorial position where there is appreciable hindrance from H(1) and H(3). (Both the salt and quaternary derivatives would be expected to be solvated by the strong Lewis base solvent.) The overall result

Table III. Calculation of Bond Charges from Bond Length and Bond Moment.

Bond	Bond Length (Å)	Bond Moment(D)	Bond Charge(e)[a]
+ -			
H - C	1.09	0.4	0.07
C - N	1.49	0.45	0.06
H - N	1.00	1.31	0.27
C_{sp^3}- C_{sp^3}	1.54	0	0

[a] $\text{Bond charge (e)} = \dfrac{\text{bond moment (D)}}{\text{bond length (Å)}} \times \dfrac{1}{4.8\ \text{e.s.u.}}$

where $e = 4.8 \times 10^{-10}$ e.s.u.

and $D = 10^{-18}$ e.s.u. cm $= 10^{-10}$ e.s.u. Å

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Table IV. Calculation of Point Charge

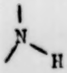
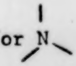
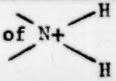
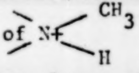
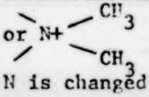
point charge for 		point charge for 	
H(1)	+ 0.07	H (1)	+ 0.07
C(9)	-0.07 X 3 = -0.21	C(9)	- 0.07 X 3 = -0.21
H(9)	+ 0.07	H (9)	+ 0.07
N	-0.06 -0.06 - 0.27 = -0.39	N	-0.06 - 0.06 - 0.06 = -0.18
H(N)	+ 0.27	C(N)	0.06 - 0.07 X 3 = -0.15
C(3)	+ 0.06-0.07 X 2 = -0.08	C (3)	+ 0.06 - 0.07 X 2 = -0.08
in the case of  only the point charge of N is changed + 1 -0.39 = + 0.61		in the case of  or  only the point charge of N is changed + 1 - 0.18 = + 0.82	

Table Va: Calculation of Sign of $^{1}L_{b}$ CD Band for Secondary Amine Salts $>NH_2^+$

Sign of A for							
M - helicity:				P - helicity:			
s	e_s	$x_s^i y_s^i z_s^i$	$e_s^i x_s^i y_s^i z_s^i$	s	e_s	$x_s^i y_s^i z_s^i$	$e_s^i x_s^i y_s^i z_s^i$
H(1)	+0.07	+1	+0.07	H(1)	+0.07	+1	+0.07
C(9)	-0.21	-1	+0.21	C(9)	-0.21	-1	+0.21
3[H(9)]	+0.21	-1	-0.21	3[H(9)]	+0.21	-1	-0.21
N^+	+0.61	-1	-0.61	N^+	+0.61	+1	+0.61
H(N)	+0.27	-1	-0.27	H(N)	+0.27	+1	+0.27
C(3)	-0.08	-1	+0.08	C(3)	-0.08	+1	-0.08
	$\sum_s e_s^i x_s^i y_s^i z_s^i = -0.73$			$\sum_s e_s^i x_s^i y_s^i z_s^i = +0.87$			
Result:	negative CD			positive CD			

Table Vb: Calculation of Sign of $^{1}L_{b}$ CD Band for Tertiary Amine Salts $\gt$NHMe^{+} and Quaternary Salts $\gt$N(Me)$_{2}^{+}$

Sign A for							
M - helicity:				P - helicity:			
s	e_s	$x_s^i y_s^i z_s^i$	$e_s x_s^i y_s^i z_s^i$	s	e_s	$x_s^i y_s^i z_s^i$	$e_s x_s^i y_s^i z_s^i$
H(1)	+0.07	+1	+0.07	H(1)	+0.07	+1	+0.07
C(9)	-0.21	-1	+0.21	C(9)	-0.21	-1	+0.21
3[H(9)]	+0.21	-1	-0.21	3[H(9)]	+0.21	-1	-0.21
N^+	+0.82	-1	-0.82	N^+	+0.82	+1	+0.82
C(N^+)	-0.15	-1	+0.15	C(N^+)	-0.15	+1	-0.15
C(3)	-0.08	-1	+0.08	C(3)	-0.08	+1	-0.08
	$\sum_s e_s x_s^i y_s^i z_s^i$ =	-0.52			$\sum_s e_s x_s^i y_s^i z_s^i$ =	+ 0.66	
Result:	negative CD			positive CD			

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must be that the conformation shown is the most stable one for 8·HBr.

The HCl salts or methiodides of the tetrahydroisoquinoline alkaloids 1-9 and 14 shown in Table II are all known to have the (S)-configuration and, like 8·HCl, all show a positive CD at 280 nm. They may therefore be assumed to possess the same, i.e. P- helicity, as compound 8·HCl. The pseudo-axial conformation of the C(1) substituent in these tetrahydroisoquinoline alkaloids thus resembles that also found in the corresponding tetralins.[23-25]

S(-)-Benzoquinolizidine·HCl 17, a cyclic analogue of 1,2-dimethyl tetrahydroisoquinoline, also exhibits a positive ^1L_b CD band at 280 nm.[26] This suggests a cis fusion at the ring junction and, of the two possible cis forms, it is the one with P- helicity 17a that is more favored when the possibility of solvation from the polar solvent used is considered.

The alkaloid S-(-)-argemonine 18 possesses two exactly identical chromophores which are the same as that of the simple tetrahydroisoquinoline alkaloids. It has been shown[27] to exhibit a positive CD for the ^1L_b band at 280 nm. As NMR data[28] have confirmed that the piperideine ring possesses the P- helicity (18a), this serves as another example of the existence of P- conformation in the piperideine ring.

Molecular orbital calculations[29] have shown that there are two equivalent MO's localized on the ether oxygen atom (two lone pair electrons) each projecting above and below the C-O-C plane. In 10·HBr, the methylenedioxy- linkage exerts such a strain that changes in bond angles and bond lengths of the benzene ring are caused, so that the ring is distorted, with M-helicity (16b). From the X-ray data of 10·HBr, a negative ^1L_b CD band can be predicted for the S- configuration. The data shown in Table II verified that both 10 and 11 have the same negative CD owing to the methylenedioxy- linkage at C(7) and C(8).

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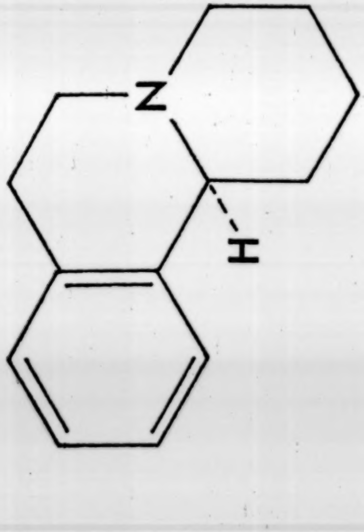

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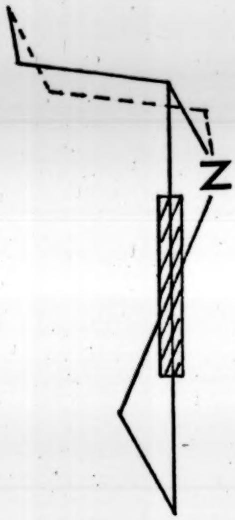
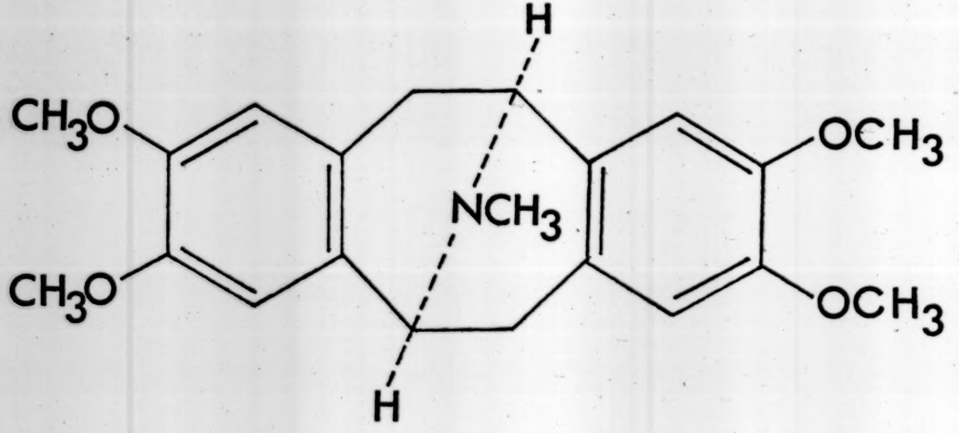


17a



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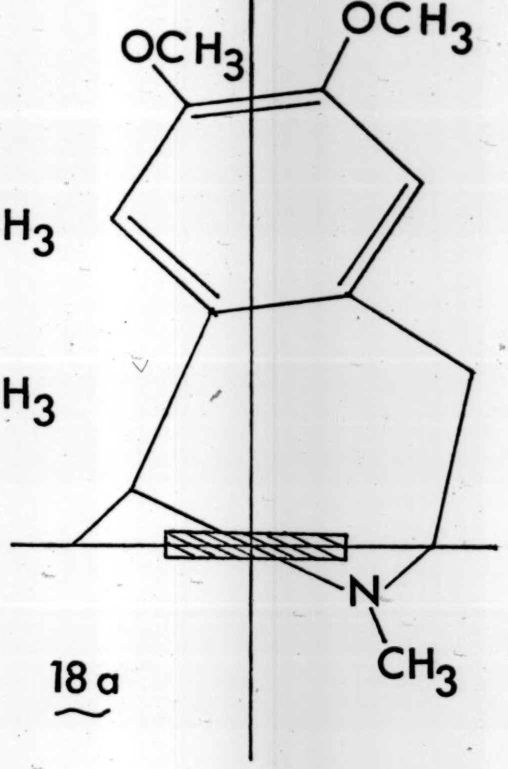

18 a

The above results indicate that most 1-methyltetrahydroisoquinoline alkaloids (specifically compounds **1**-**9** and **14**) normally exist in the P-helicity. For these, Table V predicts that the absolute S-configuration will correspond to a positive sign of the ^1L_b CD band for the protium salt or quaternary salt. Such a conclusion is independent of the oxygenation pattern of the benzene ring and the position of the substituents. In the case of the 7,8-methylenedioxy compounds **10** and **11**, X-ray data indicate, and CD measurements confirm, that the compounds have M-helicity with corresponding sign inversion of the ^1L_b CD band.

Absolute Configuration Assignment for Natural Anhalonidine and Pellotine

In his original work, Späth reported[30] that the alkaloids anhalonidine and pellotine obtained from peyote were optically inactive. Later, Späth and Kesztler[31] synthesized a pellotine sample with slight optical activity after tartaric acid resolution, which however rapidly racemized on standing. This suggests that the alkaloids may be optically active in the plant but racemize during the extraction procedure. So far, optically active anhalonidine and pellotine have not yet been reported, and therefore no absolute configuration assignments have been made for these compounds. Out of a number of samples of natural anhalonidine and pellotine we investigated, one preparation [isolated from the plant by Dr. Ara Paul (University of Michigan) by means of ion exchange chromatography][32] proved to be optically active. Natural (-)-anhalonidine·HCl showed a strong negative CD signal at 280 nm (Fig. 5). Natural (-)-pellotine, however, possessed a weak rotation of only -1.1° at the sodium D-line. In order to obtain a better

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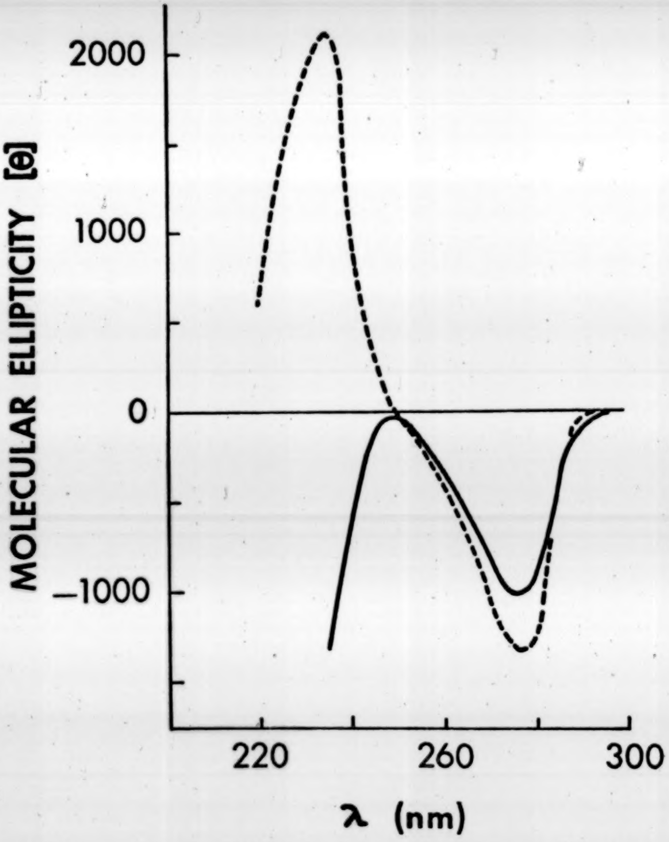

Fig. 5. CD Spectra of (-)-anhalonidine·HCl (———) and (-)-pellotine·HCl (-----).

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result for configurational assignment, natural anhalonidine was methylated with $NaBH_3CN/HCHO$ to give (-)-pellotine, $[\alpha]_D$ -11.1° showing a negative CD at 280 nm (Fig. 5). This indicated that the sample of natural pellotine was only 9-10% optically pure, having racemized to an appreciable extent during isolation. Nevertheless, the conversion of natural (-)-anhalonidine into (-)-pellotine is sufficient to establish the configurational identity of these two alkaloids, here described for the first time in optically active forms. From the negative sign of the CD at 280 nm, both belong to the R-series (assuming them to have the normal P- conformation, analogous to compounds **1**-**9** and **14**).

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CHAPTER II

CHIROPTICAL PROPERTIES OF 2-SUBSTITUTED PIPERIDINES AND A SIMPLE HELICITY RULE[1]

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Abstract: The CD spectra of fifteen 2-substituted piperidines $\underset{\sim}{2}$ and their N-methylated derivatives $\underset{\sim}{1}$ have been determined. The signs of the Cotton effects observed for the $n \rightarrow \sigma^*$ transition of nitrogen are shown to be correlated, for a given absolute configuration, with the axial or equatorial orientation of the nitrogen lone pair. The screw sense of the helicity between the nitrogen lone pair and the 2-substituent R in $\underset{\sim}{1}$ and $\underset{\sim}{2}$ determines the sign of the Cotton effect: for compounds of the absolute D configuration (=S), a positive helicity gives a positive CD while a negative helicity results in a CD of like sign.

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The longest wavelength transition of saturated aliphatic and heterocyclic amines is the n → σ^* transition involving a nonbonding orbital of nitrogen and the σ^* orbital of the C-N bond. This transition, which is located near 200 nm, disappears on protonation.[3] Early ORD measurements[4] on coniine and 2-methylpiperidine showed that the n → σ^* transition of piperidines is optically active, and subsequent work on the absolute configuration of several piperidine alkaloids[5] demonstrated for the first time that the Cotton effect (C.E.) of the n → σ^* transition of nitrogen could be observed directly by CD.

The present study is concerned with the determination of the CD spectra of a series of optically active 2-substituted piperidines 2a and their N-methyl derivatives 1a. The data so obtained are then correlated with the absolute configurations and conformations of these molecules, and a simple helicity rule is proposed to account for the observed phenomena.

Results and Discussion

The CD data for 15 piperidines are given in Tables I and II. These include a number of well-known natural products[6] and their N-methyl derivatives. All the compounds listed in Tables I and II are related to D-pipecolic acid, as shown in the Fischer projection 1b. Since the N → σ^* transition requires the presence of a lone pair of electrons on nitrogen, the CD in every case vanished completely on protonation. Measurements were made in 95% alcohol and (in a few cases) in cyclohexane. The alcohol 1a, R = n - $(CH_2)_{11}OH$ is derived from the macrocyclic spermidine alkaloid oncinotin[3] 3 and was employed to assign the absolute configuration of 3 as L by chiroptical correlation with 1-methyl-coniine. It had been demonstrated earlier[4,5] that the hydroxyl function did not interfere in this assignment.

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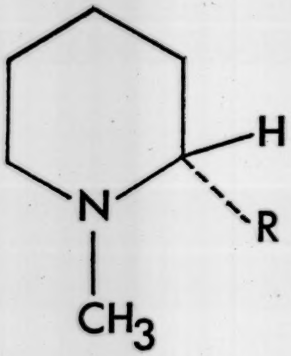

1a

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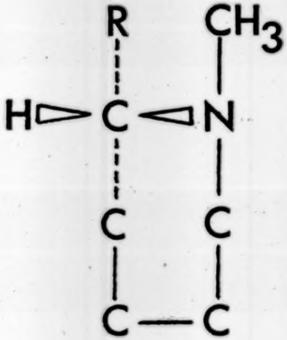

1b

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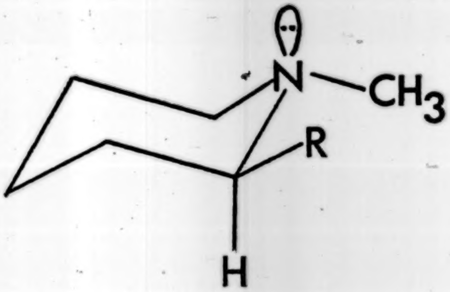
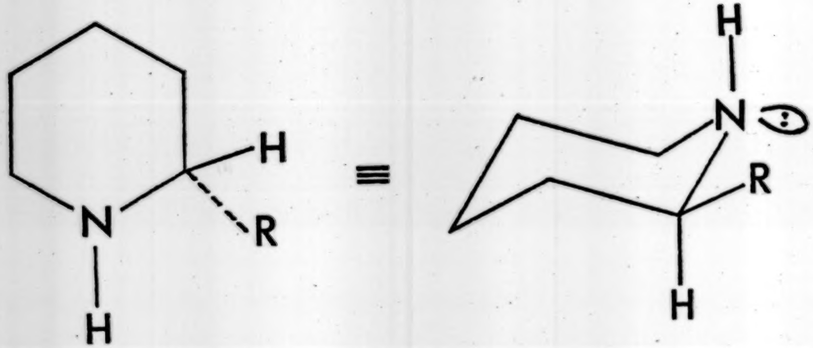


1c



2a

2b

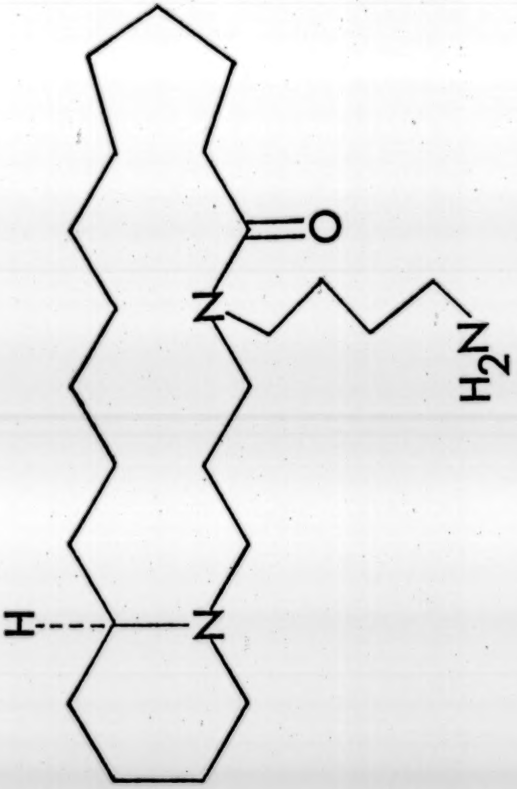


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Table I. Circular Dichroism of N-Methyl Piperidines **1a**.

Compound		**1a**, R =	$[\alpha]_D^a$	$[\theta]^a$	λ_{max}(nm)
D-(+)-1-Methylpipecoline	(S)	CH_3	+44.5°	+900	205!
D-(+)-1-Methyl-2-ethylpiperidine	(S)	C_2H_5	+72.3°	+2880	188!
		C_2H_5	+82.3°[b]	+3560[b]	204
D-(+)-1-Methylconiine[c]	(S)	n-C_3H_7	+74.9°	+3110	200!
D-(+)-1-Methyl-pipecolinol	(R)	CH_2OH	+14.7°	+1000	200!
D-(+)-1-Methyl-2-(11'-hydroxyundecyl)-piperidine[c]	(S)	n-$(CH_2)_{11}OH$	+21°	+4500	197!

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[a] Measurements are in 95% alcohol unless otherwise stated.

[b] Measured in cyclohexane

[c] Measured as the L-enantiomer. For consistency of presentation, the data given are for the D-form.

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Table II. Circular Dichroism of NH Piperidines 2a.

Compound		2a, R =	$[\alpha]_D$[a]	$[\theta]$[a]	λ_{max}(nm)
D-(+)-Pipecoline	(S)	CH_3	+7.3°	+4670	190!
D-(+)-Pipecoline	(S)	CH_3		+9075[b]	202!
D-(+)-2-Ethyl-piperidine[a]	(S)	C_2H_5	+6.6°	-730	205
		C_2H_5	+16.9°[b]	-4930[b]	227
D-(+)-Coniine	(S)	n-C_3H_7	+5.0°	-630	205
D-(+)-2-n-Butyl piperidine[c]	(S)	n-C_4H_9	+7.5°	-860	204
D-(-)-Pipecolinol	(R)	CH_2OH	-16.9°	-1140	200
D-(+)-2-(2'-Hydroxyethyl)-piperidine[c]	(R)	CH_2CH_2OH	+2.3°	-690	205
D-(-)-Sedridine	(R)	(R)-$CH_2CH(OH)CH_3$	-27.5°	-518	205
D-(+)-Allosedridine	(R)	(S)-$CH_2CH(OH)CH_3$	+17.0°	-915	205
D-(-)-Conhydrine	(R)	(R)-$CH(OH)C_2H_5$	-9.3°	-1917	198
D-(-)-Halosaline	(R)	(R)-$CH_2CH(OH)C_3H_7$	-19.5°	-548	209

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[a] Measurements are in 95% alcohol unless otherwise stated.

[b] Measured in cyclohexane

[c] Measured as the L-enantiomer. For consistency of presentation, the data given are for the D-form.

Like the $n \rightarrow \pi^*$ transition of the carbonyl chromophore,[8] the $n \rightarrow \sigma^*$ transition of nitrogen shows a prominent blue shift of about 20 nm on going from a non-polar (cyclohexane) to a polar (95% alcohol) solvent, with a concomitant decrease in intensities (Fig. 1). In the case of the $n \rightarrow \pi^*$ transition, the polar solvent tends to stabilize the nonbonding orbital more than the antibonding orbital, resulting in a blue shift of the spectrum.[8] The same argument may be applied to the $n \rightarrow \sigma^*$ transition of the cyclic amines **1** and **2**.

The lone pair of electrons on nitrogen produces a permanent dipole in the molecule. In a polar solvent, intermolecular dipole interaction is greatly reduced, particularly in the presence of hydrogen-bond forming solvent molecules, leading to a more random orientation of the solvated piperidine molecules. On the other hand, when the solvent is nonpolar (cyclohexane), the piperidine molecules will tend to arrange themselves in a stacked form with opposing dipoles so as to give a dimer with minimum dipole surrounded by nonpolar solvent molecules. Since the more rigid structure is generally known to produce higher ellipticity than randomly oriented ones, the increase in CD intensity of the cyclohexane solution as compared to an ethanolic solution (Fig. 1) thus indicates that association of piperidine monomers may occur in the nonpolar solvent.

It has been established by NMR[9] and several other physical methods[10] that the piperidine system exists in a nearly perfect cyclohexane chair conformation. Two processes may be operative in this system: ring reversal and inversion of nitrogen. As the NMR spectrum of the piperidine ring protons consists of two fairly sharp peaks at temperatures above -10°C, both processes must be fast on the NMR time scale.[11]

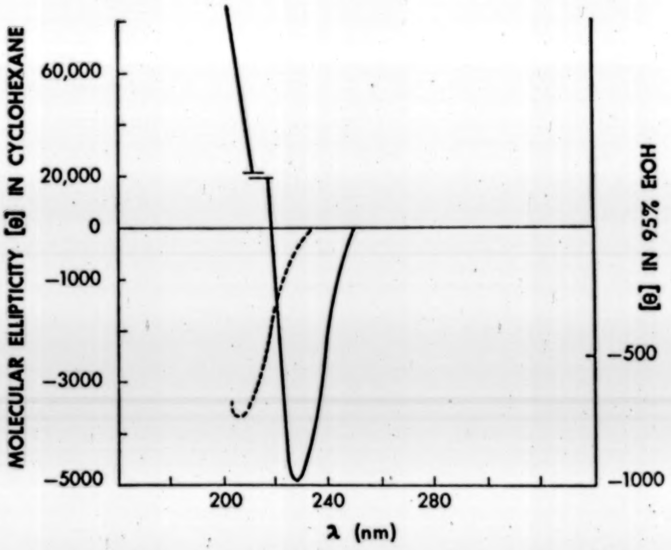

Fig. 1. CD Spectra of D-(+)-2-ethyl-piperidine in 95% Ethanol and Cyclohexane.

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For 2-alkylsubstituted piperidines of both types $\underset{\sim}{1}$ and $\underset{\sim}{2}$, the α-substituents are generally assumed to occupy the equatorial position in order to minimize steric interactions between the neighboring ring substituents. This has been confirmed by several studies using both ^{1}H-n.m.r.[12] and ^{13}C-n.m.r.[13-15] The same has been shown for α-substituents in the piperazine ring.[16]

It has been well documented[10,11,14,15,17,18,20,21] by several different methods that the methyl group in N-methylpiperidines has a decided preference for the equatorial position, with an axial lone pair of electrons as shown in Fig. 2, where the Newman projection is drawn looking at the asymmetric center and along the C-N bond.

All the N-methylpiperidines shown in Table I have a positive C.E. in the 200 nm region. Although the maximum could not be reached in 95% alcohol solution, use of cyclohexane as solvent made it possible to observe the CD maximum located at 204 nm. Assuming a solvent shift of ca. 20 nm, this could place the CD maximum in alcohol at ca. 185 nm, in reasonable agreement with the fact that this CD maximum was not reached at 188 nm.

Table II gives the CD data for the compounds of type $\underset{\sim}{2}$ possessing an NH group. With the exception of D-(+)-pipecoline ($\underset{\sim}{2}$, R = CH_3), all substances show a negative C.E. with a maximum at ca. 205 nm. Using cyclohexane, a similar solvent shift (ca. 20 nm) to longer wavelengths was observed.

In the case of D-(-)-pipecolinol and D-(-)-conhydrine, intramolecular hydrogen bonding from the OH of the α-hydroxy substituted sidechain R to the amino group is probably responsible for the blue shift of the CD maximum (ca. 5 nm). This may be caused by the lowering of the ground state energy of the nonbonding orbital of nitrogen. The greater rigidity of the hydrogen-bonded structure also results in an increased value of the ellipticity for these two compounds.

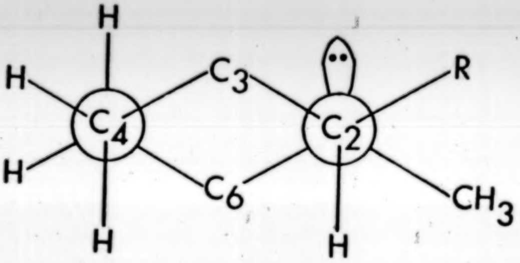

FIGURE 2

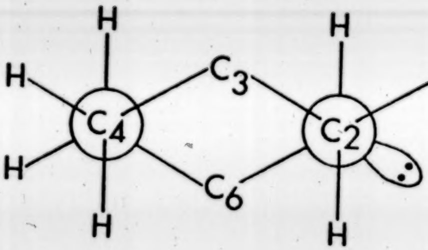

FIGURE 3

Fig. 2. Newman Projection of 1.

Fig. 3. Newman Projection of 2.

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In the piperidine series of type $\underset{\sim}{2}$, D-(+)-pipecoline presents itself as a special case. Not only does its CD have the opposite sign (Table II), but also the CD maximum is shifted to shorter wavelengths (below 190 nm) in alcohol solution. This blue shift was also apparent in cyclohexane. It therefore appears to be the only compound in Table II which resembles in its CD properties the 1,2-disubstituted compounds of type $\underset{\sim}{1}$ (Table I). It should be noted that its N-nitroso derivative shows the same CD anomaly (sign of C.E. opposite to that of all other α-substituted N-nitroso compounds of the same configuration).[19]

In the NH piperidines $\underset{\sim}{2}$, solvent molecules will interact with the lone pair on nitrogen. Such solvation will probably be more effective when the lone pair is equatorial, since the solvated electron pair will be bulkier than the NH proton. In addition, an α-substituent larger than a methyl group may be expected to offer more steric interference to the efficient solvation of the axial electron pair than to that of an equatorial electron pair. For this reason, the most favored conformation for the 2-substituted NH piperidines $\underset{\sim}{2}$ when R is greater than methyl will be that with an NH axial preference and an equatorial electron pair, as shown in Fig. 3, drawn in the same way as Fig. 2.

In the case of $\underset{\sim}{2}$, R = CH_3, the size of the α-substituent is apparently not large enough to cause interference with solvation of the axial lone pair, which is therefore able to retain its axial conformation, with an equatorial NH. This is confirmed by ^{13}C nmr evidence in the case of 2,5-dimethylpiperidine[14] and by comparison of 2-methylpiperidine and quinolizidine.[15]

If compound $\underset{\sim}{2}$, R = CH_3 thus preserves its axial lone pair of electrons, it thereby falls into the group of 2-substituted piperidines shown in Fig. 2 and its CD spectrum may be expected to conform in sign and wavelength with those shown in Table I.

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The CD maximum of 2-alkylpiperidines with an equatorial electron pair $\underset{\sim}{2}$ is thus generally found at higher wavelength (205 nm) than that of those with an axial electron pair $\underset{\sim}{1}$ (< 200 nm). This generalization also applies to 2-methylpiperidine which from other evidence is thought to have an axial electron pair, and in which λ_{max} is < 200 nm for the CD.

Although this means that the energy difference between the non-bonding orbital of nitrogen and the anti-bonding orbital of the C-N bond is greater for the $n \rightarrow \sigma^*$ transition of that conformation in which the electron pair is axial compared with that in which the electron pair is equatorial, a meaningful interpretation of this fact must wait theoretical treatment of the $n \rightarrow \sigma^*$ transition of the amino group. Comparing Figs. 2 and 3, it can be seen that the relative positions of the lone pair electrons and the α-substituent R are opposite for the two cases. In Fig. 2, if one draws an arrow from the lone pair to the α-substituent, using the pathway with smaller dihedral angle, it traces out a clockwise (positive) screw sense, while in Fig. 3, it produces a counter clockwise (negative) screw sense. Empirically, these screw senses may be correlated with the signs of the Cotton effect, i.e. a clockwise screw sense indicating a positive Cotton effect, and a counter clockwise screw sense a negative Cotton effect.

The signs of the Cotton effects may then be correlated with the absolute configuration as follows: For compounds with the absolute D-configuration (S), a negative screw sense of the helicity predicts a negative CD , while a positive one predicts a like sign of the CD.

The inversion of sign of N-H compounds relative to the corresponding N-Me compounds can thus be accounted for by the preference of the position of the electron pair and since 2-methyl piperidine has the same spatial orientations of the C(2)-Me and electron pair as 1,2-dimethyl-piperidine, they should also exhibit the same CD sign, as observed.

It is of interest that, inspite of the fact that compound of type **1** and **2** gave oppositely-signed CD maxima for the *same* absolute configuration (Tables I and II), all compoundsof the L-series give negative plain ORD curves below 225 nm in alcohol[4,7] whether they are of type **1** or **2**. It should be noted that the ORD curve of L-(-)-coniine (R) *in water* shows a weak but distinct *positive* C.E. in the 200 nm region, confirming the positive CD maximum found at the same wavelength.[22] Thus, the absolute configuration of L-(-)-2-ethylpiperidine (R) was correctly established[19] by comparison of its ORD spectrum with L-(-)-2-methylpiperidine (R) as reference compound. The sign of the CD maximum of **1** and **2** in the 200 nm region, corresponding to the $n \rightarrow \sigma^*$ transition of nitrogen,is therefore governed by the dihedral relationship between the lone electron pair on N and the α-substituent R, and is related to the screw sense of the helicity in the manner shown above. Therefore, assuming the preferred equatorial position of the sidechain R in both **1** and **2**, it will be the axial or equatorial nature of the lone electron pair (i.e. the conformation) which will be the deciding factor in the helicity and hence in the sign of the CD. While the CD is therefore conformation-dependent, the ORD curve is the result of the summation of the total $(\sigma \rightarrow \sigma^*)$ rotational contributions below 200 nm, to which the lone pair of N does not contribute, and in alcohol therefore appears to be independent of conformational changes.

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Experimental

The CD and ORD measurements were carried out on a Roussel-Jouan Mark II dichrograph and on a Jasco ORD-CD5 at room temperature. C.D. values are recorded as molecular ellipticity units [θ] and are given only for maxima or the lowest wavelengths measured.

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CHAPTER III

CHIROPTICAL PROPERTIES AND CONFORMATION OF PELLETIERINE AND ANAFERINE

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ABSTRACT:

Although the closely related D-(-)-anaferine **2** and D-(-)-pelletierine **1** have the same absolute configuration as shown by oxidative degradation, the sign of the Cotton effect for the carbonyl $n \rightarrow \pi^*$ transition cannot be used for configurational assignment as it is opposite for these two compounds. The conformation is decisive as evidenced from the sign change for pelletierine base in water and in ethanol. If the carbonyl chromophore is removed, either by ketal formation (as for pelletierine) or by reduction (as for anaferine), the resulting bases show $n \rightarrow \sigma^*$ transitions with the sign of the Cotton effect in agreement with the known model compounds D-(+)-coniine or D-(-)-sedridine in the α-substituted piperidine series. This transition may therefore be used to assign the configuration of **1** and **2**, provided that the absorption due to the $n \rightarrow \pi^*$ transition can be removed, and the remaining CD signal can be shown to be due to the $n \rightarrow \sigma^*$ transition only, by its disappearance on acidification.

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The alkaloid (-)-pelletierine 1 [1-(2-piperidyl) propan-2-one] has been shown to have the D configuration (=R) by the isolation of L-(-)-pipecolic acid on chromic acid oxidation of (+)-pelletierine,[1] while the closely related natural anaferine[2] [1,3-bis(2-piperidyl) propan-2-one] appears to be the _meso_ isomer.[3] However, since it has been reported[4] that the resolved enantiomers of anaferine racemize readily, and that under the same conditions the racemate is converted into the _meso_-form[5] in aqueous solution, it remains possible that natural anaferine is one of the optically active forms and undergoes isomerization during the isolation procedure. Since resolved (-)-1,3-bis-(2-piperidyl)propan-2-one yielded D-(+)-pipecolic acid on chromic acid oxidation,[6] resolved (-)-anaferine possesses the D,D-configuration (= R, R) 2.

From recent work on the ORD and CD spectra of 2-alkylpiperidines[7] it is clear that the negative plain curve below 225 nm found (in addition to a negative Cotton effect at 280 nm for the $n \rightarrow \pi^*$ transition of the ketone) in an earlier ORD spectrum of (-)-pelletierine sulfate[8] is due to the $\pi \rightarrow \pi^*$ absorption of the ketone and cannot be used for configurational assignments by comparison with 2-alkylpiperidines. However, such a comparison can be made if the rotational contribution of the ketone chromophore is removed by chemical means which do not interfere with the asymmetric center.

The keto group in (-)-pelletierine sulfate was converted to the dimethyl ketal by reaction with methanolic hydrogen chloride[9] at room

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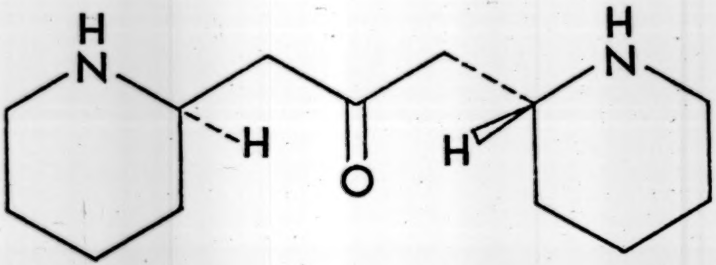

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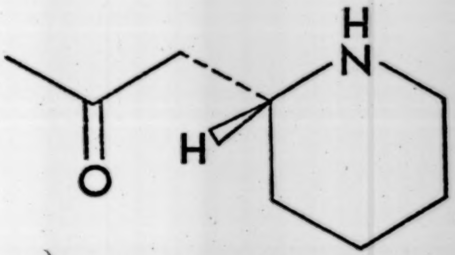

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temperature. The resulting solution then showed a negative plain ORD curve below 230 nm (Table I) and no CD between 200-300 nm because the $n \rightarrow \sigma^*$ transition of nitrogen does not exist in acidic solution. After the ice-cooled solution was made alkaline with methanolic sodium methoxide, and precipitated sodium chloride removed, it had a positive plain ORD curve, and a negative CD maximum below 208 nm. The absence of a CD band in this region in the ketal hydrochloride demonstrated that the CD maximum found in the ketal base was due to the $n \rightarrow \sigma^*$ transition of nitrogen and not to a contribution from the carbonyl chromophore. Both the negative CD and the positive ORD plain curve observed for the ketal base are in agreement with the chiroptical properties of D-(+)-coniine (Table I) and serve to confirm the D-configuration for natural (-)-pelletierine.

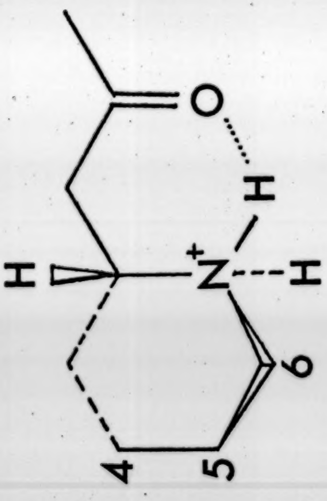
Since the absolute configuration of (-)-pelletierine is known, it is possible to use the octant rule[10] to study the conformational preference of this molecule. Assuming the piperidine ring to be in the more stable chair form[11] and equatorially substituted at C-2,[12] pelletierine sulfate can form two six-membered pseudo-ring structures through H-bonding with the carbonyl oxygen: one with a trans-fused (3a) and the other with a cis-fused ring junction (3b). The trans-fused conformation has C-5 and C-6 in the front upper left octant and is predicted to give a negative Cotton effect, while the cis-fused structure contains C-4,5 and 6 in the front lower left octant, leading to the prediction of a positive Cotton effect. Since the CD spectrum shows a negative C.E. of about the same magnitude in both 95% ethanol and in water (Table I), the trans-fused pseudo-ring

Table 1. ORD and CD spectra.

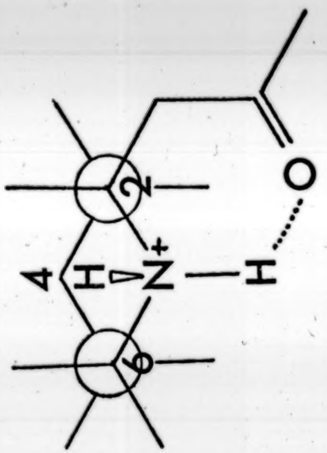
Compound	Solvent	Molecular Ellipticity	Molecular Rotation [Φ]	
		$[\theta]_{max}$ (nm)	peak (nm)	trough (nm)
D-(-)-Pelletierine sulfate	95% EtOH	-365 (281)	+180 (264)	-314 (298)
"	H_2O	-290 (272)	-760 (258)	-930 (282)
D-(-)-Pelletierine base	95% EtOH	-127 (285)	-25 (260)	-238 (295)
"	H_2O	+140 (292)	-9.5 (305)	-162 (280)
D-(-)-Pelletierine dimethyl ketal·HCl	MeOH	0 (208-300)		
D-(-)-Pelletierine dimethyl ketal base	MeOH	-158 (208!)	+284 (210!)	
D-(-)-Anaferine 2 HCl	95% EtOH	+276 (287)[a]		
Reduced Anaferine 2 HCl	MeOH	0 (203-300)		
Reduced Anaferine base	MeOH	-4700 (203!)[a]	+9800 (198!)	-690 (217)
D-(+)-Coniine[b]	95% EtOH	-630 (205)	+1900 (200!)	
D-(+)-Allo-Sedridine	95% EtOH	-915 (205)		
D-(-)-Sedridine	95% EtOH	-518 (205)		

[a] Corrected for optical purity.

[b] $[\alpha]_D$ + 5.0° (c 2.95% EtOH).



3a



3b

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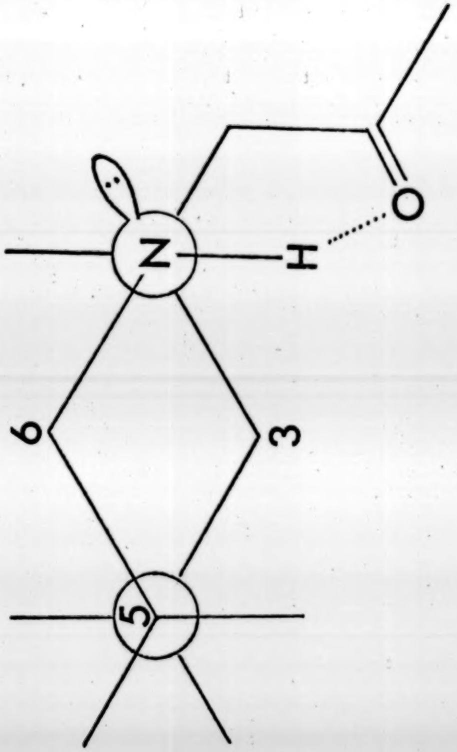
structure 3a appears to be preferred at room temperature, by analogy with other systems, e.g. decalin[13] and quinolizidine,[12d, 14] in which the cis-fused conformation is less stable than the trans-fused one. The hypsochromic shift (from 281 to 272 nm) observed with the change from a less polar to a more polar solvent is in agreement with the properties of the $n \rightarrow \pi^*$ transition.[15]

The CD and ORD of (-)-pelletierine base in 95% ethanol, measured immediately after basification of the salt, showed essentially the same features as the salt but with much reduced magnitude (Table I). This may be ascribed to the much greater availability for H-bonding of the NH protons in the salt (where the electrons of the NH bond are pulled towards the charged nitrogen atom) than in the free base. The more strongly H-bonded and therefore more rigid structure of the protonated form is reflected in the higher magnitude of the Cotton effect of the salt relative to that of the base.

Although the magnitude of the $n \rightarrow \pi^*$ Cotton effect for (-)-pelletierine base in water is of the same order as in ethanol, the sign is reversed (Table I). The assumption[4] that the contribution of the C=O chromophore in acid does not differ significantly from that in alkaline medium does therefore not appear to be correct. In the highly polar aqueous medium, solvation of the nitrogen electron pair will favor that conformation of the piperidine ring in which the electron pair is equatorial, leaving the carbonyl oxygen to form the cis-fused pseudo-ring structure 4, leading to the positive Cotton effect predicted from the octant rule for this conformation. The observed red shift in the position of this CD (Table I) suggests that the energy levels involved in this transition may be much closer in the cis-form 4 than in the trans-form in which the electron pair is axial.



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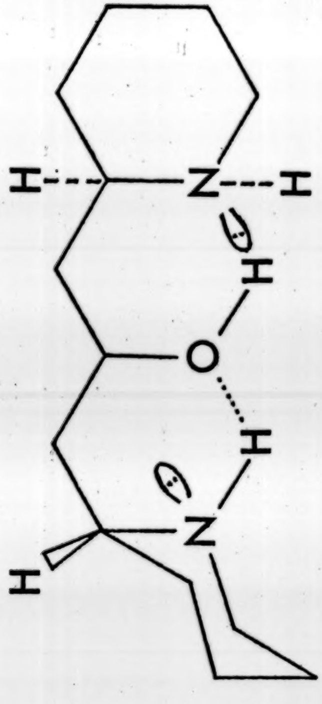
Unlike (-)-pelletierine, (-)-anaferine (2) resisted several attempts to form the dimethyl ketal, probably due to steric factors. However, reduction proceeded rapidly by catalytic hydrogenation and gave a product which (as the dihydrochloride salt) showed no CD in the range 200-300 nm, indicating complete disappearance of the carbonyl chromophore (Table I). On making the solution alkaline, the base displayed a strong negative CD in the 200 nm region confirmed by a negative Cotton effect in the same range in its ORD spectrum (Table I). Both these observations are in agreement with the CD and ORD findings for D-(+)-coniine (Table I), and confirm the established configuration of (-)-anaferine (2) as D,D (=R, R). The greatly enhanced ellipticity obtained here (as compared to coniine) suggests that greater rigidity of this diamino-alcohol is obtained through H-bonding occurring concurrently between the N_1-H and oxygen and between the electron pair on N_2 and the H of the hydroxyl group, as shown in 5. In this way, reduced anaferine resembles the alkaloids sedridine[7a] and allo-sedridine[7a] in which similar (though weaker) H-bonding may exist, as shown in 6.

The CD spectrum of (-)-anaferine dihydrochloride (2·2 HCl) shows this to have a positive ellipticity for the $n \rightarrow \pi^*$ carbonyl transition (Table I) of about the same magnitude as (-) pelletierine sulfate but of opposite sign. Assuming, as in pelletierine, that H-bonding occurs to form a trans-fused pseudo-ring structure analogous to 3a, the second piperidine ring may be expected to orient itself to give the most extended conformation (by rotating about the $C_2' - C_3'$ bond) such that the two positively-charged nitrogen atoms are the greatest distance apart, as shown in 7. The contribution to the sign of the $n \rightarrow \pi^*$ Cotton effect from the first ring will be negative



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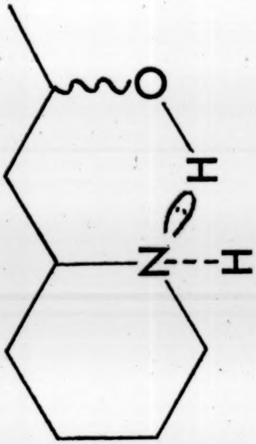

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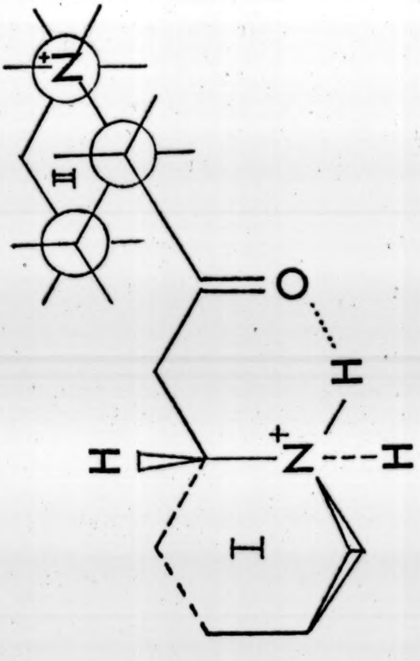

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[C(5) & C(6) in the front upper left octant] whereas the contribution of the second ring is positive, the whole ring being in the back lower right octant. These two contributions would partially cancel each other, and ring II clearly has a greater effect giving the observed positive ellipticity.

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Experimental:

ORD and CD curves were measured at 25°C on a JASCO ORD-CD 5 spectropolarimeter and on a JOUAN 185 Mark II dichrograph.

Pelletierine dimethyl acetal.--A solution of 5.6 mg of natural (-)-pelletierine sulfate, $[\alpha]_D$ - 29.5° (c 1, H_2O), in 3 ml of methanol was treated with 1 drop of 10 N - HCl. After standing at 25°C for 20 hrs, the CD signal at 280 nm had essentially disappeared. The solution was then cooled to 0°C (ice) and made alkaline with sodium methoxide to liberate the free base. After removal of precipitated sodium chloride, the solution was immediately used for CD measurement.

Reduction of Anaferine.--A solution of 23.4 mg of (-)-anaferine dihydrochloride, $[\alpha]_D$ - 22.1° (c 0.8 EtOH), in 3 ml of 95% ethanol was reduced with Adam's catalyst (PtO_2) and hydrogen. The solution was filtered, cooled to 0°C (ice), and the filtrate made alkaline with 10% aqueous KOH and used immediately for CD measurement.

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Acknowledgment

We are grateful to Dr. L. Marion for a sample of natural pelletierine and to Drs. H. Beyerman and L. Maat for a sample of resolved anaferine.

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CHAPTER IV

STUDIES IN THE CHIROPTICAL PROPERTIES OF SELENOAMINO ACIDS[1]

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Abstract: The circular dichroism (CD) spectra of four selenium-containing amino acids were investigated and compared with those of their sulfur and methylene analogues. In the region 190-250 nm, positive Cotton effects of carboxyl and selenide (or sulfide) chromophores always correlate with L(=S) or L,L(=S,S) absolute configurations. The additive nature of such Cotton effects was demonstrated by a "difference curve" method, which permits the chiroptical properties of the Se (or S) chromophore to be determined. Results suggest that the C-Se-C selenide chromophore has three optically active transitions in the near UV range at approximately 225, 210 and 195-200 nm.

The absolute configuration of natural (+)-selenocystathionine has been established spectroscopically to be L,L (=S,S), in agreement with enzymatic results.

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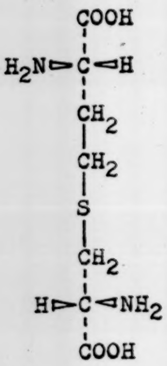
INTRODUCTION

Selenoamino acids first attracted interest during the latter part of the 1930's when it was shown that a cattle disease known as "alkali disease", found in parts of the United States, was closely connected with the selenium content of the soil, that plants were capable of accumulating selenium, and that the selenium so incorporated occurred in the protein fraction of the plants (3,4). Selenoamino acids were isolated from the plant material (5) and proved to be highly toxic (6).

These findings led to the synthesis of selenoamino acids by Fredga (7) and by Zdansky (8). Walter and Roy (9) have reviewed the selenopeptides and selenoproteins, an undiscovered territory only a decade ago.

Optically active selenocystathionine 2 has been isolated from plant material (10, 11) and was found to possess biological effects. Its absolute configuration was assigned as L on the basis of the lack of reactivity with D-amino acid oxidase (11). However, the selenium compound could have inhibited the enzyme.

Since no chiroptical studies of selenoamino acids have been made, we decided to investigate this subject. Among the physical methods used for obtaining information on chiroptical properties, the technique of circular dichroism (CD) measurement is the most efficient since it gives precise data on the chirality of specific transitions. The acids under investigation contain two chromophores which absorb in the near UV region: COOH and C-Se-C. References on simple carboxyl absorption indicate that the $n \rightarrow \pi^*$ transition occurs at approximately 210 nm and a $\pi \rightarrow \pi^*$ transition below 190 nm (12). However, few literature references exist for the C-Se-C selenide chromophore.



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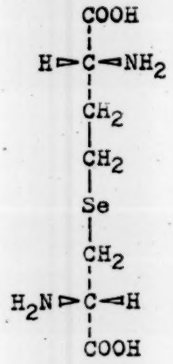

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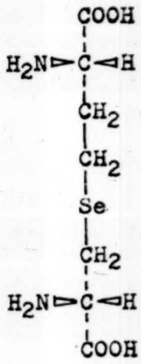

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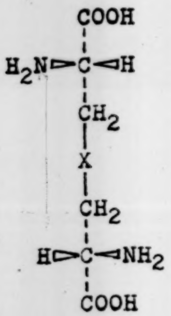
The solution spectrum (hexane) of diethyl selenide (13) reveals an absorption band at 250 nm (ϵ_{max} 50). In the similarly constituted dialkyl sulfides, the C-S-C sulfide chromophore has recently been shown (14,15) to have several electronic transitions between 198 and 255 nm. The $n \rightarrow \sigma^*$ transitions of the C-Se-C chromophore may therefore be expected to occur in the same region as the $n \rightarrow \pi^*$ transition of COOH.

RESULTS AND DISCUSSION

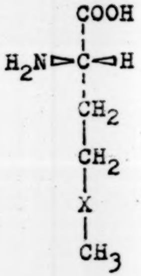
We studied the CD properties of the following optically active selenoamino acids: selenocystathionine 2 and its allo diastereomer 3, selenolanthionine 4b, and selenomethionine 5b. In order to have a better understanding of the experimental results, we also carried out measurements on the corresponding sulfur analogues cystathionine 1, lanthionine 4a, methionine 5a, cysteine 6a and its S-methyl derivative 6b, and on their methylene analogues α,ε-diaminopimelic acid 4a and 2-aminobutyric 7a, -valeric 7b, and -caproic 5c acids. The position of the CD maxima and the corresponding ellipticity values are given in Table I for all compounds. It was observed that selenoamino acids, like other amino acids (16), exhibit a red shift of the CD when the pH changes from the alkaline to the acidic region; all CD data were therefore recorded at pH 1 in aqueous solution as the hydrochloride salts. This also establishes standard conditions for comparing chiroptical contributions from the COOH chromophore in different molecules, since protonation of the amino group abolishes any contribution from the $n \rightarrow \sigma^*$ transition of free NH_2. Unlike some acids which have S attached directly to the asymmetric center (17), the compounds shown in Table I exhibit relatively simple CD spectra. In the 190-250 nm



4a (X = S)

4b (X = Se)

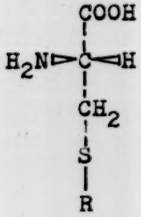
4c (X = CH_2)



5a (X = S)

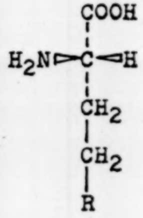
5b (X = Se)

5c (X = CH_2)



6a (R = H)

6b (R = CH_3)



7a (R = H)

7b (R = CH_3)

Table 1. Intensity and Position of Cotton Effects of Amino Acids used in CD Studies[a]

Compound	[θ]	λ_{max}(nm)
L-(+)-selenomethionine 5b	5480	206
L-(+)-selenolanthionine 4b	3580	220
	8420	200
D-(-)-selenocystathionine 2	-9990	201
D-(+)-alloselenocystathionine 3	4440	216
L-(+)-cysteine 6a	5130	208
L-(-)-S-methyl cysteine 6b	5130	223
	2320	205 (shoulder)
L-(+)-methionine 5a	4060	205
L-(+)-lanthionine 4a	9220	217.5
L-(+)-cystathionine 1	6050	217.5
	9160	200
L-(+)-2-aminobutyric acid 7a	3150	207.5
L-(+)-2-aminovaleric acid 7b (norvaline)	3900	207.5
L-(+)-2-aminocaproic acid 5c (norleucine)	3880	207.5
L,L-(+)-α,ε-diaminopimelic acid 4c	6850	204
(+)-selenocystathionine (natural product	11290	200

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[a] All compounds were measured in 0.2N HCl except (+)-seleno-cystathionine (natural product) and L,L-(+)-α,ε-diaminopimelic acid which were measured in 0.1N HCl.

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region, where contributions from COOH and S-C or Se-C are both present, positive Cotton effects are always related to S(=L) or S,S(=L,L) configurations. This permits the assignment of absolute configuration of new selenium- or sulfur-containing amino acids (Table I). Even in a molecule containing two asymmetric centers of opposite configuration, e.g. D-alloselenocystathionine 3, the absolute configuration at each chiral center can be determined by the difference curve method which will be discussed in the following sections.

The CD spectrum of L-selenolanthionine·2HCl 4b is shown in Fig. 1. Of the four selenoamino acids measured, this is the only one which exhibits a complex CD curve, suggesting that there are at least two Cotton effects present, at 200 and 220 nm respectively. Present knowledge of the electronic states of selenium-containing compounds is very limited, whereas sulfur and carboxyl transitions have been well studied. Since sulfur and selenium are both group VI elements, it is informative to compare the chiroptical behavior of L-selenolanthionine 4b with that of its sulfur analogue, L-lanthionine 4a (Fig. 1).

Jung et al (16) recorded the CD spectra of several sulfur-containing amino acids and investigated their pH and temperature dependence. They reported, and our measurements confirm, that the CD of L-lanthionine at pH 1 consists of a broad positive band centered at 218 nm, regarded as a superposition of two bands; the shorter wavelength band being attributed to the carboxyl transition and the higher wavelength portion belonging to a sulfur transition. In view of recent reports (14,15) that there are at least three optically active transitions present in compounds containing the C-S-C (sulfide) chromophore, it was possible that the conclusion of Jung et al was oversimplified. A CD measurement on L,L-α,ε-diaminopimelic acid 4c, which is the

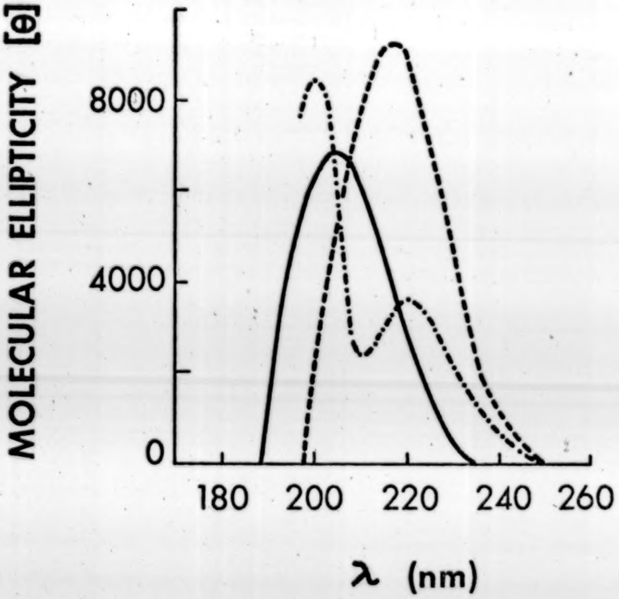

Fig. 1. CD Spectra of

L-(+)-lanthionine•2HCl 4a (-----),

L-(+)-selenolanthionine•2HCl 4b (-·-·-) and

L,L-(+)-α,ε-diaminopimelic acid•2HCl 4c (——).

methylene analogue of L-lanthionine 4a, showed a simple positive CD maximum as a narrow band centered at 204 nm (Fig. 1). Since the methylene group shows no UV or CD contribution between 185-250 nm, the difference between the CD spectra of 4a and 4c was replotted as shown in Fig. 2 and represents the chiroptical contribution due to the C-S-C sulfide chromophore. The difference curve shows a negative CD at 197 nm and a positive CD at 223 nm. These results are in excellent agreement with Salvadori's report (14) of transitions at 201-210 nm (negative), 229-230 nm (positive) and 246-250 nm (small negative) for open-chain sulfides of the S-configuration, when the difference in the solvents used is taken into consideration. Our measurements were recorded in aqueous solution while those for the open-chain sulfides (14) were in heptane solution. Since sulfur transitions are $n \rightarrow \sigma^*$ in nature, a polar solvent would stabilize the nonbonding orbitals and cause a blue shift of the spectrum. The shift observed here is approximately 6-10 nm towards shorter wavelengths, the positive 229-230 nm band being shifted to 223 nm and the negative 201-210 nm band to 197 nm. The greater magnitude of the 223 nm band relative to that at 197 nm[*] explains the absence of the very small oppositely signed CD band at long wavelengths and of the shoulder observed at shorter wavelength, and leaves only the 197 nm band observable.

Having thus demonstrated that the "difference curve" method could be useful in providing the general feature of a CD spectrum for open chain sulfides, the method was next applied to L-selenolanthionine 4b. The difference curve

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[*] due presumably to the different nature of the perturbing groups in the open-chain sulfides of Salvadori (14) and in the present compounds.

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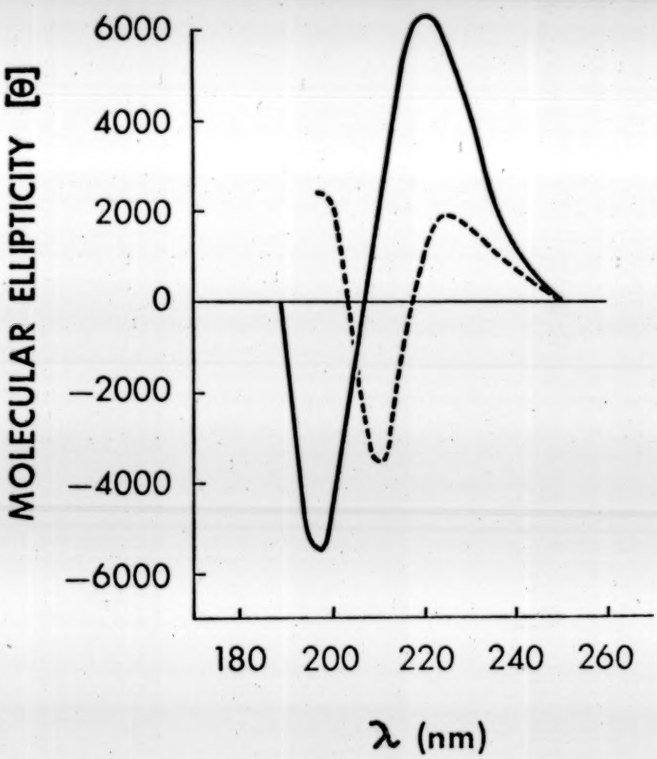

Fig. 2. CD Difference Curves for L-(+)-lanthionine·2HCl $\underset{\sim}{4a}$ & L,L-(+)-α,ε-diaminopimelic acid·2HCl $\underset{\sim}{4c}$ (———) and L-(+)-selenolanthionine·2HCl $\underset{\sim}{4b}$ & L,L-(+)-α,ε-diaminopimelic acid·2HCl $\underset{\sim}{4c}$ (-----).

(Fig. 2) between the CD spectra of 4b and 4c suggests that there are at least three optically active transitions for the C-Se-C selenide chromophore in the range 190-250 nm. Optically active open-chain selenides which do not have any other chromophore in the molecule have not yet been reported. On the basis of symmetry considerations and semi-empirical calculations, Rosenfield and Moscowitz (15) proposed an assignment for the three lowest lying optically active C-S-C transitions. The first two lowest lying transitions are from a nonbonding 3p sulfur orbital to antibonding orbitals between sulfur and carbon atoms. These are the $n \rightarrow \sigma^*$ transitions. The third band is assigned as an atomic-like transition which involves electron excitation from a nonbonding orbital to a 3d atomic orbital of sulfur only. Since Se and S have similar atomic character, the three Cotton effects observed for the Se contribution (Fig. 2) could probably also be accounted for by an analogous rationale except that the molecular orbitals involved here consist of different atomic orbitals, namely, the nonbonding 4p and 4d atomic Se orbitals.

D-selenocystathionine 2 and D-alloselenocystathionine 3 are diastereomers that differ in the absolute configuration of one of the two asymmetric carbons. The CD spectra of these two acids are shown in Fig. 3. Both spectra have only one CD maximum. However, because of the difference at one asymmetric center, not only are the Cotton effects of opposite sign, but the positions of their maxima also differ by 15 nm. If one takes the difference of the two structures 3 and 2, the contributions of the two identical asymmetric centers would cancel out, and one would be left with two L-selenomethionine-like molecules. The CD difference curve is therefore expected to be twice that of L-selenomethionine 5b (*vide infra*). The "difference curve" is shown in Fig. 4 together with the CD spectrum of L-selenomethionine, multiplied by 2. The excellent agreement

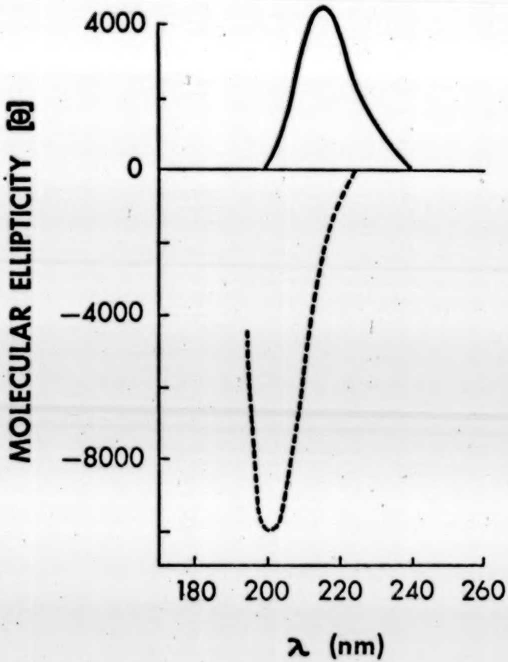

Fig. 3. CD Spectra of

D-(-)-selenocystathionine·2HCl 2 (-----) and

D-(+)-alloselenocystathionine·2HCl 3 (——).

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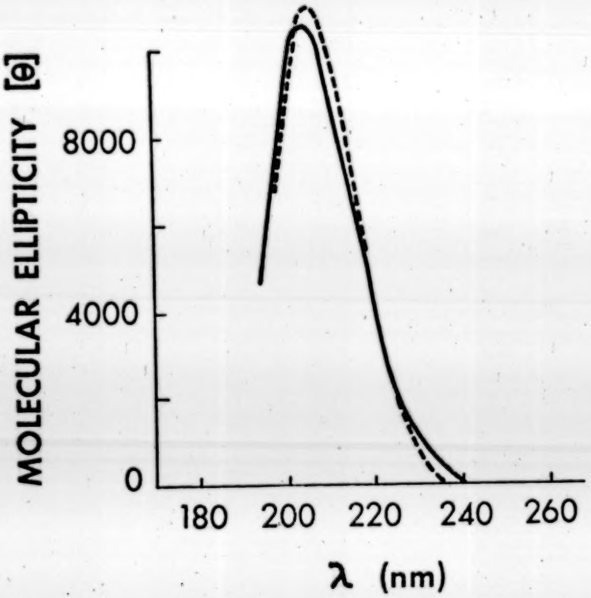

Fig. 4. CD Spectrum of L-(+)-selenomethionine·HCl 5b multiplied by two (-----) and CD Difference Curve for D-(+)-alloselenocystathionine·2HCl 3 & D-(-)-selenocystathionine·2HCl 2 (———).

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on position and magnitude of the two CD curves in Fig. 4 thus illustrates the additive nature of the Cotton effects related to the selenide and carboxyl chromophores, and shows that two asymmetric centers separated by 4 atoms are far enough apart to have little or no interactions electronically. Similar conclusions drawn from CD measurements on sulfur-containing amino acids have been arrived at by Jung *et al* (16). Therefore it is possible to assign the absolute configuration of both of the two asymmetric centers of a pair of selenium-containing amino acid diastereomers such as 2 and 3 by a CD study as follows: a) The CD difference curve (3 minus 2) is equal to twice that of L-selenomethionine 5b. At the two asymmetric centers which are different in 3 and 2, 3 therefore has the L- and 2 must have the D-configuration. b) Since the Cotton effects are additive in nature, and the contribution due to the $n \rightarrow \pi^*$ transition is larger than that due to the selenide chromophore (*vide infra*), that compound in which both asymmetric centers have the same configuration will have the larger Cotton effect. In this case, compound 2 (Table I) will therefore have the D-configuration also at the other asymmetric center.

The CD spectra of the closely analogous L-selenomethionine 5b and L-methionine 5a show apparently simple positive CD maxima corresponding to the L-configuration as does their methylene analogue L-2-aminocaproic acid 5c (Table I). In order to reveal the chiroptical contribution of the heteroatom (S or Se) in 5b and 5a, a "difference curve" method is again employed for comparison, and the results are shown in Fig. 5. Whereas in the L-selenolanthionine series (4a and 4b) the heteroatom (S or Se) is separated by one carbon from the asymmetric center, in the two acids 5a and 5b the heteroatom (S or Se) is two carbons away from the center of asymmetry. This difference in structure not only decreases the magnitude of the ellipticity due to S or Se, it also reverses the sign of each

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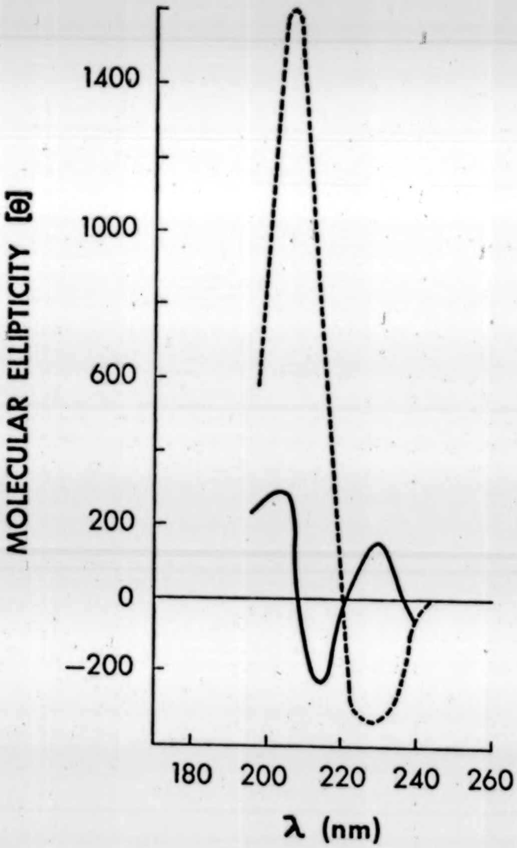
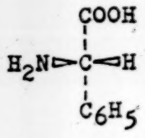
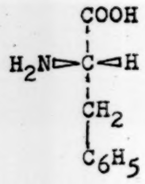


Fig. 5. CD Difference Curves for L-(+)-methionine·HCl 5a & L-(+)-2-aminocaproic acid·HCl 5c (———) and L-(+)-selenomethionine·HCl 5b & L-(+)-2-aminocaproic acid·HCl 5c (-----).



$H_2N-C(H)(COOH)-C_6H_5$

8



$H_2N-C(H)(COOH)-CH_2-C_6H_5$

9

Cotton effect due to S or Se, compared to those shown in Fig. 2. The decrease in ellipticity can be understood on the basis of first order perturbation theory. The reversal of the sign of the Cotton effects, although unexpected, finds an analogy in the L-amino acid derivatives $\underset{\sim}{8}$ and $\underset{\sim}{9}$ which also show a reversal of sign (18) when an additional methylene group is inserted between the asymmetric center and the observed chromophore, in this case the 260 nm band of benzene. Similar inversion of the Cotton effect for the carbonyl chromophore (19) has been analyzed in terms of a conformational equilibrium change (20).

Natural (+)-selenocystathionine, isolated from the seeds of Lecythis Ollaria (9, 10, 11) is not attacked by D-amino acid oxidase and on the basis of this negative enzymatic reaction has been assigned the L,-L-configuration (11). Due to the unknown effect of selenium on enzymes, such a negative result does not unambiguously prove the absolute configuration. However, its CD is seen (Table I) to be the mirror image of that of synthetic D-selenocystathionine. The stereochemistry of the natural product can thus be confirmed as L, L.

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Experimental

CD measurements were made on a Roussel-Jouan Dichrograph II CD spectrometer at pH 1 in aqueous solution at room temperature. CD curves were recorded in terms of molecular ellipticity units $[\theta]$. CD data are given below for the zero line intersections, lowest wavelengths measured, and for the maxima and shoulders observed.

L-(+)-selenomethionine·HCl. $[\alpha]_D^{23.5}$ + 13.0° (c 0.038, 0.2 N HCl). CD (c 0.038, 0.2 N HCl), $[\theta]_{235}$ 0, $[\theta]_{206}$ + 5480, $[\theta]_{198}$ + 3490.

L-(+)-selenolanthionine·2HCl. $[\alpha]_D^{23.5}$ + 29.2° (c 0.0257, 0.2 N HCl). CD (c 0.0257, 0.2N HCl), $[\theta]_{250}$ 0, $[\theta]_{220}$ + 3580, $[\theta]_{210}\overset{+2320,}{\wedge}[\theta]_{200}$ + 8420, $[\theta]_{197}$ + 7580.

D-(-)-selenocystathionine·2HCl. $[\alpha]_D$-37.7° (c 0.0305, 0.2 N HCl). CD (c 0.0305, 0.2 N HCl), CD (c 0.0305, 0.2N HCl), $[\theta]_{225}$ 0, $[\theta]_{201}$-9990, $[\theta]_{195}$-4440.

D-(-)-alloselenocystathionine·2HCl. $[\alpha]_D^{26}$ - 9.8° (c 0.0254, 0.2N HCl). CD (c 0.0254, 0.2N HCl), $[\theta]_{240}$ 0, $[\theta]_{216}$ + 4440, $[\theta]_{200}$ 0.

L-(+)-cysteine·HCl $[\alpha]_D^{25}$ + 5.1° (c 2, 5N HCl). CD (c 0.436, 0.2N HCl), $[\theta]_{250}$ 0, $[\theta]_{208}$ + 5130, $[\theta]_{195}$ + 3340.

L-(-)-S-Me-cysteine·HCl $[\alpha]_D^{20}$ - 9.5° (c 0.058, 0.2N HCl). CD (c 0.058, 0.2N HCl). CD (c 0.058, 0.2N HCl), $[\theta]_{250}$ 0, $[\theta]_{223}$ + 5130, $[\theta]_{205}$ + 2320, $[\theta]_{197.5}$ 0, $[\theta]_{195}$-1550.

L-(+)-methionine·HCl. $[\alpha]_D^{19}$ + 19.2° (c 0.0573, 0.2N HCl). CD (c 0.0537, 0.2N HCl), $[\theta]_{240}$ 0, $[\theta]_{205}$ + 4060, $[\theta]_{195}$ + 2560.

L-(+)-lanthionine·2HCl. $[\alpha]_D$ + 3° (c 5, 2.4N NaOH). CD (c 0.0648, 0.2N HCl), $[\theta]_{250}$ 0, $[\theta]_{217.5}$ + 9220, $[\theta]_{197.5}$ 0.

L-(+)-cystathionine·2HCl. $[\alpha]_D^{23}$ + 23.1° (c 1, 1N HCl). CD (c 0.0298, 0.2N HCl), $[\theta]_{245}$ 0, $[\theta]_{217.5}$ + 6050, $[\theta]_{212}$ + 5400, $[\theta]_{200}$ + 9160 $[\theta]_{191.5}$ 0, $[\theta]_{190}$ -1960.

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L-(+)-*2-aminobutyric acid·HCl*. $[\alpha]_D^{21}$ + 13.3° (c 0.548, 0.2N HCl). CD (c 0.548, 0.2N HCl), $[\theta]_{245}$ 0, $[\theta]_{207.5}$ + 3150, $[\theta]_{193}$ + 1560.

L-(+)-*2-aminovaleric acid·HCl*. $[\alpha]_D$ + 16.01° (c 0.3, 0.2N HCl). CD(c 0.3, 0.2N HCl), $[\theta]_{245}$ 0, $[\theta]_{207.5}$ + 3910, $[\theta]_{195}$ + 2450.

L-(+)-2-*aminocaproic acid·HCl*. $[\alpha]_D$ + 15.20° (c 0.296, 0.2N HCl). CD (c 0.296, 0.2N HCl), $[\theta]_{245}$ 0, $[\theta]_{207.5}$ + 3885, $[\theta]_{195}$ + 2340.

L,L-(+)-*α,ε-diaminopimelic acid·2HCl.* $[\alpha]_D$ + 38.5° (c 2.6, 5N HCl). CD (c 0.184, 0.1N HCl), $[\theta]_{235}$ 0, $[\theta]_{204}$ + 6850, $[\theta]_{189}$ 0.

(+)-*selenocystathionine·2HCl* (natural product). $[\alpha]_D$ + 38.6° (c 0.029, 0.1N HCl). CD (c 0.029, 0.1N HCl), $[\theta]_{225}$ 0, $[\theta]_{200}$ + 11290, $[\theta]_{190}$ 0.

Acknowledgment. We are indebted to Drs. Harvey E. Alburn and Peter B. Russell for a sample of natural selenocystathionine, and to Dr. Elizabeth Work for a sample of natural α,ε-diaminopimelic acid.

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CHAPTER V

CHIROPTICAL PROPERTIES OF α-SUBSTITUTED SUCCINIC ACIDS: CONFORMATION AND ABSOLUTE CONFIGURATION[1]

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Abstract: The effect of conformational preference on the chiroptical properties of α-substituted succinic acids and esters 2 has been investigated using variable-temperature CD in solvents of different polarity. All available evidence indicates that when R' in 2 is alkyl or halogen, the preferred conformation is 1e with the $-CH_2COOR$ group eclipsed by the C = O bond, while when R' in 2 is hydroxy, methoxy, or amino, the major conformer is 1d in which the heteroatom is eclipsed by the C = O bond. In both cases, conformation 1f appears to be the least favored, mainly on steric grounds. The results when R'= chloro or bromo do not support previously proposed conclusions and an alternative explanation is advanced. In the resultant octant projection (Fig. 2) it is shown that the sign of the Cotton effect for 1 will be determined by the position of the groups X and Y in the back octants, and since one of these is always H in the two favored conformations, the sign is actually determined by the position of the other group. This octant projection predicts successfully the sign of the ellipticity of the $n \rightarrow \pi^*$ transition for any α-substituted succinic acid or ester with the appropriate substituent R', and appears to apply also to simple alkanoic acids and esters with the same substituents.

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Introduction

The electronic transitions of carboxylic acids or esters in the near UV region have received much attention during the last ten years. However, although a considerable amount of experimental data relating to the carboxyl chromophore has been generated, the development of a successful theoretical treatment of this subject is far behind that of the carbonyl transitions.[3,4] The simple carbonyl group exhibits a well known low intensity, low energy absorption near 290 nm, due to an $n \rightarrow \pi^*$ transition. It is generally believed that when -OR is attached to the carbonyl group, interaction of the nonbonding electrons on the ether oxygen with the π-orbitals of the carbonyl group raises the energy of the antibonding π-orbital and splits the bonding π-orbital into two new orbitals, π_1 and π_2, the latter being essentially a nonbonding orbital located mainly on the ether oxygen. An approximate energy diagram for the carboxyl chromophore is presented in Fig. 1.[3] The two transitions of lowest energy then belong to $n - \pi_3^*$ and $\pi_2 - \pi_3^*$.

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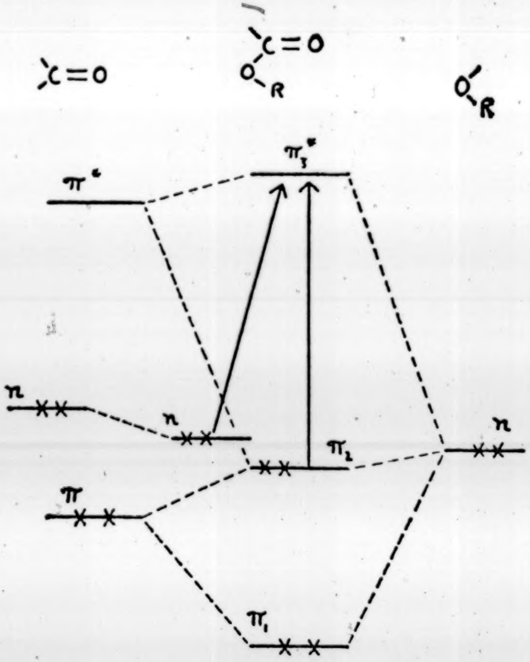
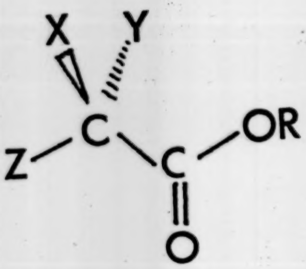


Fig. 1. Energy Level Scheme for the Ester Carbonyl System[3]

From the energy diagram, the $n \rightarrow \pi^*$ transition of the carboxyl group is predicted to appear at shorter wavelength than the corresponding ketone transition. In fact, a weak absorption band is observed to occur near 210 nm which fulfills all the criteria used[3] in the identification of $n \rightarrow \pi^*$ transitions: (a) low intensity (since it is symmetry forbidden), (b) "blue shift" of the maximum caused by electron-supplying substituents attached directly to the π-system, (c) "blue shift" of the maximum with increasing polarity of the medium, and (d) obliteration of vibrational fine structure on changing from nonpolar to polar media.

In general, CD and UV show the same or similar wavelengths of absorption maxima in the spectrum. For optically active aliphatic carboxylic acids or esters, a Cotton effect is always observed near 210 nm.[5] However, recent CD studies of α-hydroxy acids of S-(+)-configuration have shown[6-9] two optically active bands in the 200-250 nm region: the normal positive 210 nm band and an abnormal negative 245 nm band. Similar findings[9,10] were also extended to the α-amino acids, i.e. the S-(+)-acid has a small CD of opposite sign at higher wavelength which disappears on protonation of the amino group. A possible explanation for the occurrence of such a phenomenon was the existence of conformational isomerism as shown by low temperature measurements[7], leading to the conclusion that both bands belong to the same $n \rightarrow \pi^*$ transition of the carboxyl group.

An empirical treatment of the optically active carboxyl transition has led to the development of the so-called "lactone rule"[11] for the correlation of chiroptical behavior and configuration of lactones. However, due to the complex nature of the carboxyl transition, the boundaries used in this rule for Cotton effect sign assignment are very difficult to define, and the usefulness of the "lactone rule" is thereby seriously diminished. From Fig. 1, it can be seen that, for the carboxyl n → π* transition, the electrons involved are mainly localized on the carbonyl oxygen, therefore the ground state symmetry of this transition should be the same as that of the ketone chromophore. On this basis, the ketone octant rule[12] should also be applicable to optically active α-substituted acids or esters. If the octant rule is applied to an α-substituted acid (1, R=H), the sign assignment of the back octant, defined as in an α-substituted cyclohexanone,[12] would be as shown in Fig. 2. Since octant rule data are based mostly on α-halo and α-methyl substituent, we decided to examine, initially, the chiroptical behavior of some α-methyl and α-halo substituted acids and then to extend this to the study of acids with other α-substituents.



1

	X=	Y=	Z=
1a	H	CH_3	CH_2COOCH_3
1b	CH_2COOCH_3	H	CH_3
1c	CH_3	CH_2COOCH_3	H
1d	CH_2COOR	H	R'
1e	H	R'	CH_2COOR
1f	R'	CH_2COOR	H

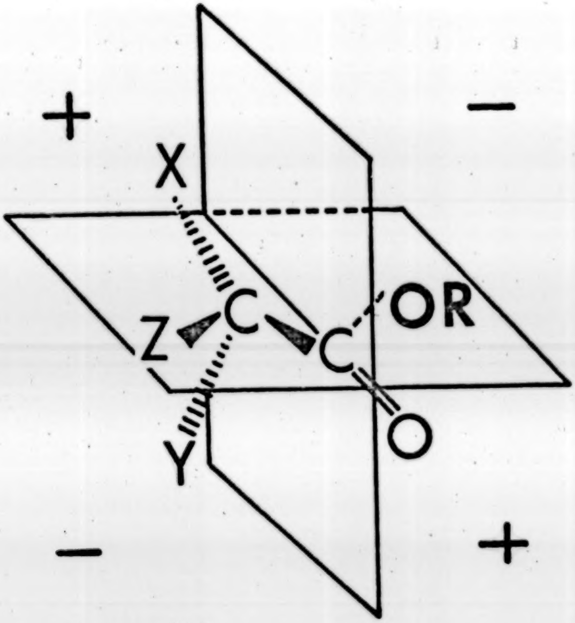


Fig. 2. Sign Assignment for Back Octants of an α-Substituted Acid or Ester 1.

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α-alkyl Succinic Acids and Esters

The simplest α-methyl substituted optically active acid that may be used for CD study would be α-methyl butyric acid (of which 1, X=H, Y=Me, Z=Et is one conformer). However, the very similar nature of the α-alkyl groups, and the resulting conformational equilibrium, would be expected to result in a low intensity CD band.[13] For this reason, we chose to investigate the corresponding α-alkyl succinic acids (1, R=H, Z=CH_2COOH) for which conformational data are available[14] showing them to exist predominantly in the extended (trans-) conformation 2 in both succinic and α-methyl succinic acid and their esters, i.e. in that conformation which possesses the minimum dipole in solution. In the free acids, strong intra- or intermolecular H-bonding exists and would cause conformational changes in both polar and nonpolar solvents, which would in turn affect the chiroptical properties of the molecule.[15] To avoid such complications, we investigated the CD of S-(-)-dimethyl α-methyl succinate (2, R=R'=Me).

Results and Discussion

CD measurements were carried out in two different solvents, 95% EtOH and cyclohexane, and at variable temperatures ranging from -20°C to 38°C. The data presented in Table I and Figs. 3a and 3b summarize the position, magnitude and sign of the ellipticity bands of S-(-)-dimethyl α-methyl succinate under various experimental conditions. Two Cotton effects of opposite sign were always observed in this study. The shorter wavelength band centered at 208 nm is much higher in intensity than the longer wavelength band of which the position of maximum ellipticity is shifted further to the visible range when the ratio of these two bands increases (Fig. 3). At a

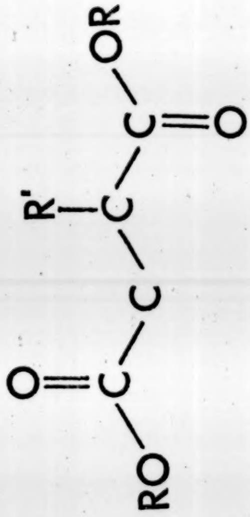

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Table I. Circular Dichroism of S-(-)-dimethyl α-methylsuccinate ($\underset{\sim}{2}$, $R=R'=CH_3$).

solvent	temperature (°C)	$[\theta]_{208}$	$[\theta]_{240}$(nm)
Cyclohexane	10	-2240	+38 (242)
"	20	-2070	+44 (240)
"	30	-1880	+53 (238.5)
"	38	-1680	+61 (237.5)
95% EtOH	-20	-3010	+5.9 (244)
"	-10	-2790	+7.0 (244)
"	-0	-2550	+9.2 (243)
"	20	-2200	+12.8 (242)

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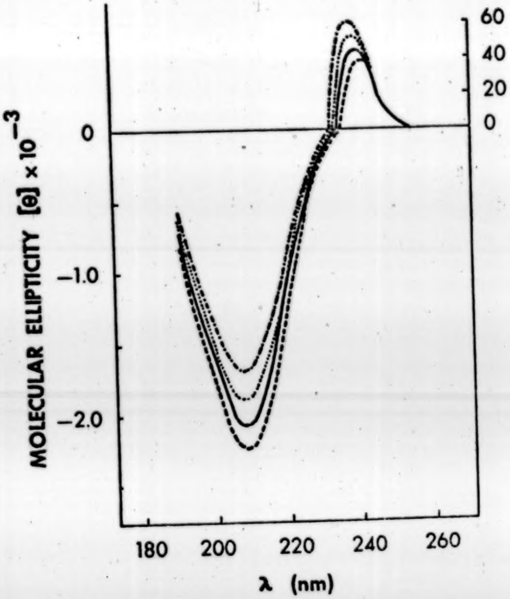

Fig. 3a. Circular Dichroism of S-(-)-dimethyl α-methylsuccinate in Cyclohexane at 10°C (-----), 20°C (———), 30°C (.....), and 38°C (-·-·-).

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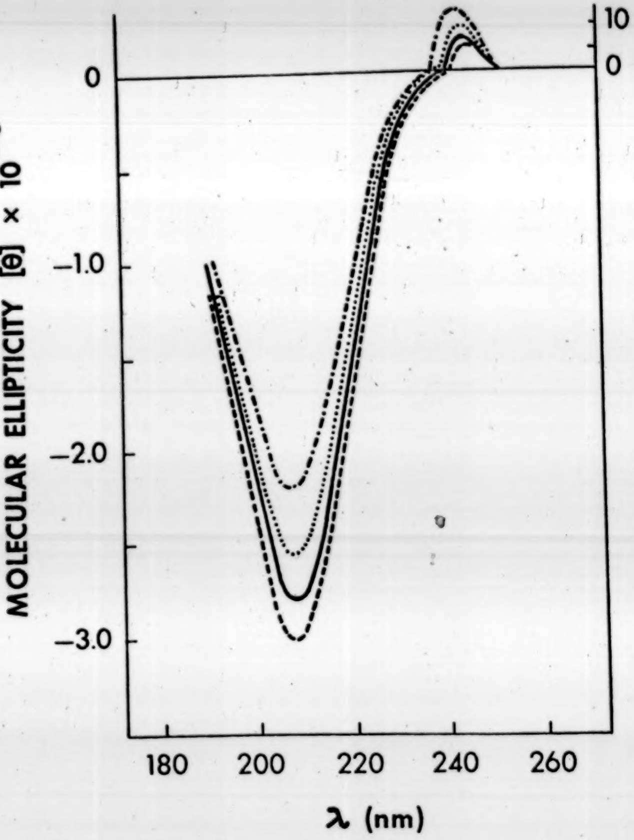

Fig. 3b. Circular Dichroism of S-(-)-dimethyl α-methylsuccinate in 95% Ethanol at -20°C (-----), -10°C (———), 0°C (•••••), and 20°C (-•-•-).

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specified temperature, e.g. 20°C, the shorter wavelength band increases in intensity in a polar solvent such as ethanol, whereas the longer wavelength band decreases. For measurements at different temperatures, it can be seen that, in both solvents, the large band increases at the expense of the small when temperature is lowered, and vice versa. Such solvent and temperature effects observed implied that the two bands are closely interrelated and are probably associated with a single electronic transition. The best possible explanation for these findings would be the existence of an equilibrium between two or more conformers of this ester in solution. According to the "bent bond" or "banana type" concept[16] of the double bond, a three fold barrier to rotation around the C_α-COOR bond is generally assumed and a staggered conformation as shown in **1** is ordinarily favored on energy consideration. For the three most likely conformers, **1a**, **1b**, and **1c**, **1c** is considered the least stable on steric grounds and **1a** is regarded as the preferred conformer. If these three rotamers are projected into the back octant of Fig. 1, **1a** contributes a negative sign, **1b** a positive sign, and **1c** a negligible contribution to the $n \rightarrow \pi^*$ transition of the ester. Combining the results from the steric point of view and the application of the octant rule, it may be concluded that **1a** is the conformation responsible for the 207 nm band and **1b** is that associated with the long wavelength band.

Extrapolation of the data in Table I to a zero value of the ellipticity for the 235 nm band (Fig. 4) in both 95% ethanol and cyclohexane gives an approximate magnitude for the CD of the lower wavelength band corresponding to 100% population of that conformer responsible for this band. For both solvents, the extrapolated value is -3300 ± 100. Calculation of the approximate free energy difference between the two conformers at 20°C gives $\Delta G = -400$ cal/mole

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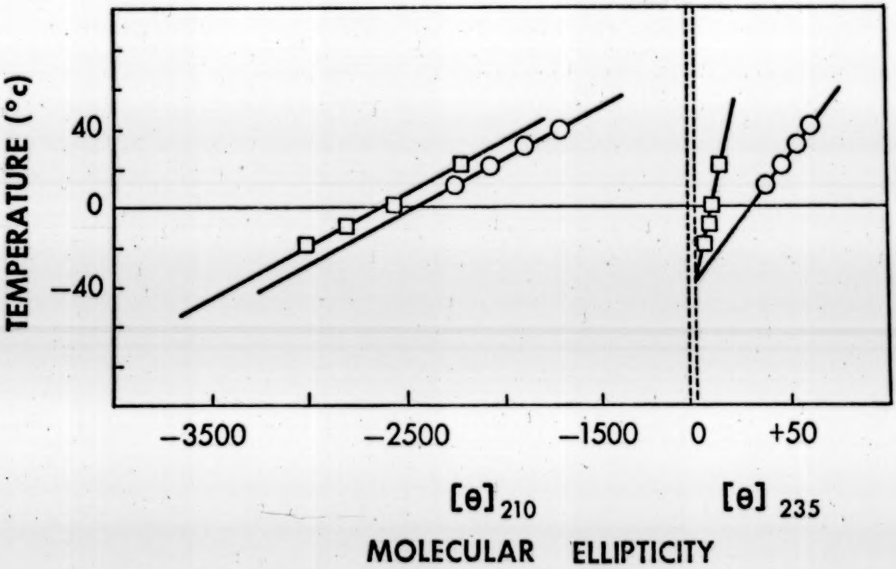

Fig. 4. Temperature-Dependence of S-(-)-dimethyl-α-methyl succinate in Cyclohexane (-○-○-) and in 95% Ethanol (-□-□-).

in 95% ethanol for the equilibrium (235 conformer ⇄ 210 nm conformer). In cyclohexane, the corresponding value of ΔG is -310 cal/mole.

At about the same time as this work was in progress, the CD of four α-alkyl succinic acids ($\underset{\sim}{2}$, R=H, R'=ethyl, butyl, isopropyl, and cyclohexyl) in water was reported.[13] A single ellipticity band near 210 nm was shown and no longer wavelength band was discerned.[13] Since these findings were not in agreement with our results on dimethyl α-methyl succinate, we re-examined a series of nine of these acids ($\underset{\sim}{2}$, R=H, R' = methyl, ethyl, propyl, butyl, pentyl, hexyl, isopropyl, cyclohexyl, and isobutyl). The results of the CD measurements in 95% EtOH are summarized in Table II. All the acids except S-(-)-isopropyl and S-(-)-cyclohexyl succinic acid showed both 210 nm and 235 nm bands of opposite sign, exactly as in the methyl ester (above). The magnitude of the higher wavelength band decreased with increasing size of the α-substituent R' and, at the same time, the rotational contribution of the R' group to the shorter wavelength band increases from methyl to isopropyl. The absence of the long wavelength band for S-(-)-isopropyl and S-(-)-cyclohexyl succinic acids can best be explained on the basis that these two acids both possess α-branched substituentswhich would result in higher energy barriers for rotation around the C_α-COOH bond and thus they exist preferentially in the lowest-energy conformation. As there is no mutual reduction of rotational strength due to another oppositely signed long wavelength band,[17] the apparent maximum ellipticity of these two acids is much higher than that of all other acids in the series (Table II). The results obtained here offer a further support to the argument given earlier for the ester, i.e. a conformational equilibrium exists in solution and from the analogous conformational analysis of S-(-)-dimethyl α-methyl succinate,

Table II. Circular Dichroism of S-(-)-α-Alkylsuccinic Acids ($\underset{\sim}{2}$, R=H, R'=Alkyl) in 95% EtOH.

R'	$[\theta]_{210}$(nm)	$[\theta]_{235}$(nm)
Methyl	-1840 (208)	+40 (239)
Ethyl	-2300 (209.5)	+13 (244.5)
Propyl	-2380 (209)	+15.5 (243.5)
n-Butyl	-2290 (209)	+11.7 (244)
n-Pentyl	-2490 (209.5)	+14.5 (246)
n-Hexyl	-2430 (210)	+13.7 (245)
Isopropyl	-4240 (211.5)	0
Cyclohexyl	-3660 (210.5)	0
Isobutyl	-2120 (208.5)	+42.7 (241)

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the most favored conformation responsible for the 210 nm band is ($\underset{\sim}{1}$, X=H, Y=R', Z=CH_2COOH) and that responsible for the 235 nm band is ($\underset{\sim}{1}$, X=CH_2COOH, Y=H, Z=R').

α-Halo Succinic Acids and Esters

To avoid possible inter- or intramolecular H-bonding which would in turn affect the chiroptical properties of the acids in solution, we investigated the CD of S-(-)-dimethyl α-chloro and α-bromo succinates in both 95% EtOH[18] and in cyclohexane. The position and magnitude of the CD absorptions are summarized in Tables III and IV. In all three solvent systems used, it was not found possible to reach the lower wavelength CD maximum of S-(-)-dimethyl α-chloro succinate even at 185 nm. Although two oppositely signed Cotton effects are demonstrated for this compound, the lack of quantitative data on the position and magnitude of the low-wavelength ellipticity, makes it impossible to draw any significant conclusion from such measurements. However, in the case of S-(-)-dimethyl α-bromo succinate, two CD maxima with opposite sign can be definitely located. The lower wavelength band, in contrast to the findings for α-methyl succinate, is much smaller in intensity than the oppositely signed long wavelength band. Variable temperature CD measurements also show a different trend of behavior: both bands increase in intensity with decreasing temperature. This strongly suggests that, unlike its α-methyl substituted analogue, S-(-)-dimethyl α-bromo succinate exhibits two different optically active transitions in the spectrum range measured. One possible explanation is that the lower wavelength CD is due to the $n \rightarrow \sigma^*$ transition[19] of C-Br and the higher wavelength CD due to the $n \rightarrow \pi^*$ transition of the carboxyl group. If the same argument is applied to the α-chloro ester,

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Table III. Circular Dichroism of S-(-)-dimethyl α-chlorosuccinate ($\underset{\sim}{2}$, R=CH_3, R'= Cl) at 20°C.

Solvent	$[\theta]_{222}$	$[\theta]_{\text{lowest wavelength}}$ measured (nm)
cyclohexane	-8460	+3550 (185)
95% EtOH	-4370	+1810 (186)
H_2O containing 10% EtOH	-3080	+1590 (185)

Table IV. Circular Dichroism of S-(-)-dimethyl α-bromosuccinate ($\underset{\sim}{2}$, R=CH_3, R'=Br).

Solvent	Temperature (°C)	$[\theta]_{235}$	$[\theta]_{202.5}$
cyclohexane	+10	-10600	+1065
	+20	-10250	+ 820
	+30	-9820	+ 740
	+38	-9530	+ 570
95% EtOH	-40	-10220	+ 730
	-20	-9490	+ 420
	0	-8700	+ 230
	+20	-8160	+ 90

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it would also explain our inability to see the low wavelength CD maximum, since the n → σ* transition of C-Cl is known[20] to be at much lower wavelength. It has been shown by UV measurements[21] that axial α-bromo ketones may undergo a red shift of ∿ 28 nm while axial α-chloroketones[22] show a red shift of ∿ 14-25 nm in relation to the parent ketone. As an extension of this α-haloketone rule, we propose that the higher wavelength band of α-bromo and α-chloro esters is an n → π* transition shifted 15-25 nm to the red by the "axial" position of the halogen α-substituent. This corresponds to a preferred conformation (1, X=H, Y=Br or Cl, Z=CH_2COOMe) in which the $C_\alpha - C_\beta$ bond eclipses the carbonyl oxygen. For this conformation, the corresponding octant projection in Fig. 2 would result in a negative CD as observed. Another possible conformation suggested from conformational analysis[23] of chloroacetaldehyde and bromoacetaldehyde is that in which the halogen eclipses the carbonyl double bond (1, X=CH_2COOMe, Y=H, Z=Cl or Br). The corresponding octant projection, however, shows it would give a positive CD, opposite to that observed. Also, solvent effects indicated that the long wavelength band increases in intensity with decreasing polarity of the solvent, which implies that the conformation responsible for this CD band is less polar in nature and therefore corresponds to (1, X=H, Y=Br or Cl, Z=CH_2COOMe) and not to the other conformer.

Saturated alkyl bromides are known[24] to give an optically active absorption near 200 nm. On the basis of UV measurements, this absorption is assigned as an n → σ* transition of C-Br. The magnitude and position of the CD band are in exact agreement with those of the low wavelength CD observed for the α-bromo succinate. To investigate the effect of temperature on this n → σ* transition, we carried out CD measurements of R-(-)-2-bromooctane at various temperatures (Table V). Surprisingly, examination of the CD

Table V. Circular Dichroism of R-(-)-2-Bromooctane.

Solvent	Temperature (°C)	$[\theta]_{203}$
Cyclohexane	+10	+860
	+20	+830
	+30	+800
	+38	+770
95% EtOH	-20	+1040
	0	+ 960
	+20	+ 900

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results revealed that the ellipticity band actually increases in intensity with decreasing temperature in both solvents used. Such observations further confirm our earlier proposed assignment of the 203 nm band of α-bromo succinate as primarily derived from the $n \rightarrow \sigma^*$ transition of C-Br.

While this work was in progress, the CD of L-(-)-α-chloro-succinic acid in water was reported[13] to give a positive CD maximum at 200 nm and a negative CD maximum at 222 nm. Since this did not agree with our results on S-(-)-dimethyl α-chloro succinate, we examined both L-(-)- α-chloro and L-(-)- α-bromo succinic acids in 95% EtOH and in water (Table VI). The results fully confirmed our previous conclusions reached for the corresponding dimethyl esters. Firstly, the CD in 95% EtOH was consistently larger than that in water for the same reason as in the esters. Secondly, for the chloro acid, it was not possible to record the low wavelength CD maximum in either alcohol or water. Our conclusions are therefore that the α-halo acids and esters exist in the same conformation ($\underset{\sim}{1}$, X=H, Y=Br or Cl, Z=CH_2COOR) in which the $C_\alpha - C_\beta$ bond is eclipsed by the C=O bond. This is confirmed by the agreement with the "axial haloketone rule" shift in wavelength of the $n \rightarrow \pi^*$ absorption maximum, by the fact that the octant rule is obeyed for this conformation to give the correct CD sign but not for the alternative one ($\underset{\sim}{1}$, X=CH_2COOR, Y=H, Z=Cl or Br),[25] and by the effects of solvent polarity changes.

Table VI. Circular Dichroism of L-(-)-chlorosuccinic acid and L-(-)-bromosuccinic acid.

2, R=H, R'=	Solvent	$[\theta]_{230}$(nm)	$[\theta]_{200}$(nm)
Cl	95% EtOH	-3970 (225)	+1530!(192)
"	H_2O	-2320 (223)	+1940! (191.5)
Br	95% EtOH	-8060 (235)	+160 (203.5)
"	H_2O	-5940 (232)	+840 (203.5)

α-Hydroxy Acids and Esters

It was shown[5] that the ORD spectra of α-hydroxy acids of the S configuration gave a single positive Cotton effect at ca. 215 nm due to the $n \rightarrow \pi^*$ transition of the carboxyl group. Anand and Hargreaves reported[6] for S-(+)-lactic acid a weak negative CD band in the 245 nm region as well as the expected strong positive CD maximum at lower wavelength. Since the CD spectrum in alkaline solution showed no negative Cotton effect, they ascribed the band at 245 nm to the $n \rightarrow \pi^*$ transition, and the strong positive maximum at 210 nm to other including $\pi \rightarrow \pi^*$, transitions of the molecule. However, Barth et al. attributed both CD bands to the $n \rightarrow \pi^*$ transition and interpreted their data by assuming that each band is associated either with different rotamers or with different solvated species. The weak 240 nm band was also found to be present in other α-hydroxy acids, their esters, and their O-methyl ethers[9,13] and was thus not due to intra- or intermolecular H-bonding. At alkaline pH values, the 240 nm CD disappeared while an unpredictable change occurs in the magnitude of the CD band at 215 nm. Listowsky et al.[13] showed that, in general, an increase in the ratio of the magnitude of the long wavelength ellipticity compared with that of the short wavelength ellipticity is observed for the α-hydroxy acids in the nonaqueous solvents; i.e. in nonpolar solvents the contribution due to the 240 nm band increases. They also observed that an increase in temperature induces an increase in the intensity of the long wavelength band near 240 nm and a concomitant decrease in the band near 210 nm, and a decrease in temperature induces the opposite effect. This behavior implies that the two bands are closely interrelated and are probably associated with a single electronic transition. On the basis of the solvent and temperature studies, they assumed that the most stable conformation is that in which the hydroxy substituent is eclipsed by the C=O bond (1, X=CH_2R, Y=H, Z=OH) and that this rotamer is responsible for the 210 nm band. It was further suggested that the conformer of structure (1, X=H, Y=OH, Z=CH_2R) generates the longer wavelength band.

To study the effect of O-substitution α to a carboxyl group, we chose to investigate the solvent and temperature dependence of the CD of S-(-)-dimethyl α-methoxy succinate, since this compound had been shown[9] to have an unusually high ratio of the 240 nm CD to that at 215 nm.

Results and Discussion

The CD of S-(-)-dimethyl α-methoxy succinate was examined over a temperature range between + 38 and - 40°C in 95% EtOH and cyclohexane (Table VII). In both solvents, an increase in temperature resulted in an increase in the magnitude of the high wavelength CD and a decrease in that of the low wavelength CD, as expected from a mixture of two conformers existing in equilibrium with each other (Fig. 5). Extrapolation of the data in Table VII to a zero value of the ellipticity for the 235 nm band gave an approximate magnitude[26] for the CD of the lower wavelength band corresponding to 100% population of that conformation. In 95% EtOH solution, this extrapolated value of the 210 nm CD was ca. +4000. From this, it was possible to calculate an approximate free energy difference between the two conformers at 20°C, $\Delta G = +100$ cal/mole for the equilibrium (240 nm conformer $\rightleftarrows$ 210 nm conformer). The smallness of the $\Delta G°$ in this case may be due to the

Table VII. Circular Dichroism of S-(-)-Dimethyl α-methoxysuccinate

Solvent	Temperature (°C)	$[\theta]_{212}$(nm)	$[\theta]_{235}$(nm)
Cyclohexane	+10	+530	-590
	+20	+500	-620
	+38	+400	-640
95% EtOH	-40	+2760 (215)	-120 (240)
	-20	+2410 (215)	-160 (240)
	0	+2120 (215)	-200 (240)
	+20	+1850 (215)	-210 (240)

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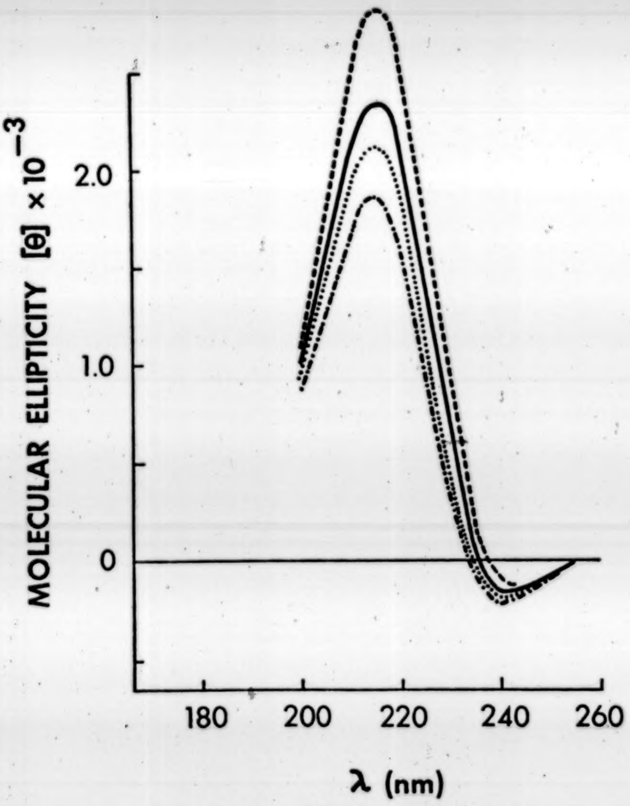

Fig. 5. Circular Dichroism of S-(-)-dimethyl α-methoxysuccinate in 95% Ethanol at -40°C (-----), -20°C (——), 0°C (•••••), and 20°C (-•-•-).

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fact that no intramolecular stabilization by H-bonding is possible in the α-OMe compound examined, and also that the increased size of the methoxy group versus the hydroxy substituent will increase the population of the non-eclipsed conformer. This seems to be supported by the reported value of a ΔG° of ca. 1.1 Kcal/mole in water at 25°C for the two corresponding conformers of L-malic acid.[13] At lower temperatures, the percentage of the 210 nm conformer increases, suggesting that the low wavelength CD is due to (1, X=CH_2COOMe, Y=H, Z=OMe). In the octant projection (Fig. 2), the sign expected from this conformer is positive, as found experimentally.

In cyclohexane solution, the similar magnitude of the two CD maxima makes it impossible to use the same extrapolation method and obtain significant results. This is due to the distortion in both magnitude and wavelength of the maxima caused by the overlap of two oppositely signed Gaussians when these are approximately equal.[17]

The increase in the intensity of the 210 nm CD band, and the decrease in that at 235 nm, as solvent polarity increases is in agreement with the view that rotamer (1, X=CH_2COOCH_3, Y=H , Z=OCH_3) is the most favored in polar solvents, being the one which interacts most strongly with polar solvents and is thus energetically favored through solute-solvent interactions. In low polarity solvents, the population of the other conformers should increase.

α-amino Acids and Esters

In addition to the strong positive CD maximum at 200-210 nm, α-amino acid esters of the L-configuration (S) show a second (smaller) negative CD band at ca. 235 nm which (unlike the lower wavelength band) does not correspond to an observed UV transition.[3,9,10,27] The fact that α-amino acid esters containing tertiary amino groups still show the abnormal (235 nm) CD band argues against intra- or intermolecular H-bonding being responsible for this band.

Results and Discussion

Our measurements on L-(+)-diethyl aspartate showed the presence of the 235 nm negative CD maximum in both 95% EtOH and cyclohexane (Table VIII). The positive CD maximum in the 200-210 nm region was apparently due to a combination of two bands of the same sign, one (at lower wavelength) due to the $n \rightarrow \sigma^*$ transition of nitrogen[28] and the other due to the normal $n \rightarrow \pi^*$ transition of the carboxyl group. This was shown e.g. by the disappearance of the lower wavelength portion ($n \rightarrow \sigma^*$) of the 200-210 nm CD band on acidification, leaving intact the normal positive band at 210 nm ($n \rightarrow \pi^*$) in the hydrochloride salt; at the same time, the 236 nm band had disappeared. For these reasons, it was not feasible to carry out temperature dependence studies on the two CD maxima corresponding to the $n \rightarrow \pi^*$ transition.

Hydrogen bonding is an important feature of the crystal structures of all the amino acids. The charged ammonium group of the zwitterion or the hydrochloride salt is an excellent H-bond donor and the carboxylate ion or the oxygen of the C=O dipole in the free acids or the esters is a good acceptor. As a result, strong H-bonds are invariably formed between these two groups, and have been found by X-ray diffraction studies.[29] Studies on amino acid conformation in the solid state, using the hydrochloride salts,[30] have shown that the amino group generally takes up the position cis to the C=O bond. In dilute solution in protic solvents, solvation will take the place of much

Table VIII. Circular Dichroism of L-(+)-Diethyl Aspartate

Solvent	Temperature (°C)	$[\theta]_{200}$(nm)	$[\theta]_{230}$(nm)
Cyclohexane	+20	+5440 (202.5)	-2180 (233)
95% EtOH	-40	+2530! (192.5)	-1600 (228.5)
"	-20	+2570! (194)	-1470 (229.5)
"	0	+2650! (196)	-1320 (230)
"	+20	+2650! (197.5)	-1280 (230.5)
95% EtOH + HCl	+20	+2230 (210)	0

of the intermolecular H-bonding. However, p-π overlap due to interaction between the amino nitrogen and the C=O bond will still tend to stabilize the amino group in the cis position to the C=O bond relative to the other conformers. Literature data[31] thus support the existence of α-amino acids predominantly in that conformation in which the α-amino group is close to being eclipsed by the C=O bond (1, X=CH_2R'', Y=H, Z=NH_2) for the L-configuration. As in the corresponding α-hydroxy compounds, there is also present some of the conformation (1, X=H, Y=NH_2, Z=CH_2R''), while the third possible conformer is the least favored on ground of steric repulsion. In the α-amino acid hydrochlorides, the conformer (1, X=CH_2R'', Y=H, Z=NH_2) will be even more favored due to intramolecular H-bonding, and this may explain the disappearance of the high wavelength (235 nm) negative CD band on acidification, and in the free (zwitterionic) amino acids themselves.[9,10]

In all reported observations, the CD of L-amino acids shows a positive maximum at ca. 215 nm, suggesting that it is due to the conformation (1, X=CH_2R'', Y=H, Z=NH_2), with a corresponding octant projection (Fig. 2) in agreement with experimental results. The conformational behavior of the α-amino acids or esters is thus very similar to that of the corresponding α-hydroxy acids of the same configuration, and it is possible that the longer wavelength band for the α-amino acids is generated by the conformer of structure (1, X=H, Y=NH_2, Z=CH_2R'').

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Conclusion

Of the three conformers **1d**, **1e** and **1f**, all available evidence indicates that when R'=alkyl or halogen in **2**, the preferred conformation is **1e**, with the $-CH_2COOR$ group eclipsed by the C=O bond, while when R'=hydroxy, methoxy or amino in **2**, they exist mainly in the conformation **1d** in which the heteroatom is eclipsed with the carbonyl group. In both cases, conformation **1f** appears to be the least favored, mainly on steric grounds.

In the resultant octant projection (Fig. 2) it is therefore clear that the sign of the Cotton effect for **1** will be determined solely by the position of the groups X and Y in the back octants. Since in conformations, **1d** and **1e**, one of the two groups, X or Y is always H, accordingly the sign is actually determined simply by the position of the other group. This octant projection thus predicts the expected sign of the ellipticity of the $n \rightarrow \pi^*$ transition in the 200-250 nm region for any α-alkyl, halo, hydroxy, alkoxy, or amino substituted succinic acids or esters **2**. These conclusions also appear to apply to the simple alkanoic acids or esters (**1**, $X=CH_2R''$, Y=H, Z=R') with the same α-substituent R', and are not in disagreement with the simple empirical rule proposed by Listowsky *et al.*[13]

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(26) Although this plot is not linear, it may be extrapolated to zero with an error not exceeding 10%.

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CHAPTER VI

CHIROPTICAL PROPERTIES AND OPTICAL AND M.O. CALCULATIONS FOR DICTYOPTERENES A AND B[1]

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ABSTRACT: Circular dichroism spectra of the optically active cyclopropane hydrocarbons **1a** and **2**, measured over a range of temperatures, showed these compounds to be configurationally identical. The CD spectrum was found to consist of two overlapping exciton pairs, corresponding to an equilibrium mixture of two solution conformers, for which thermodynamic parameters were calculated.

Optical calculations using the exciton model were used to obtain the sign of the rotational strength for the long wavelength part of the exciton pair for different conformers. The result confirmed the absolute (R, R) configuration for **1a** obtained from oxidative degradation, and the conformational assignment made from spectral analysis showing that the *trans*-*trans*-conformer is responsible for the pair of exciton bands at shorter wavelength region. Both CNDO/2 and *ab initio* calculations confirmed that this conformer was of the lowest energy.

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INTRODUCTION

The odoriferous constituents of the essential oil of algae of the genus *Dictyopteris* comprise a number of C_{11} hydrocarbons, two of which possess a trans-disubstituted cyclopropane ring. Dictyopterene A is trans-1-(trans-1-hexenyl)-2-vinylcyclopropane (1a)[3] and Dictyopterene B is trans-1-(trans, cis-hexa-1',3'-dienyl)-2-vinylcyclopropane (2).[3] Both are optically active, having $[\alpha]_D$ + 77° and -43° respectively.

Optically active cyclopropane hydrocarbons have not previously been studied, and the chiroptical properties of 1a and 2 were therefore examined in order to gain an understanding of their relation to conformational preferences and absolute configuration.

The long wavelength transitions of optically active molecules composed of two chromophores have usually been described by one of the following two models: (I) The exciton model, for cases where coupling between the chromophores is weak, e.g., homo-conjugated dienes or (II) the "inherently dissymmetric chromophore" model, for cases where coupling is strong, e.g. helicenes. In the case of the two hydrocarbons 1a and 2, we will show that their spectra can best be analyzed by a model which combines the features of both (I) and (II).

Cyclopropane has long been considered to conjugate with ethylene to a degree between that characteristic for saturated and unsaturated groups, and its presence in a molecule like 1a or 2 provides an electronic linkage between the two ethylenic chromophores. In the case of vinylcyclopropane, rotation around the bond connecting the cyclopropane

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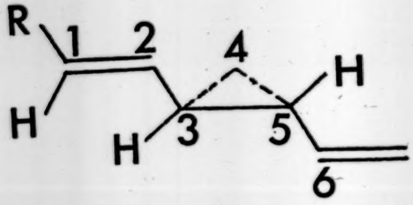
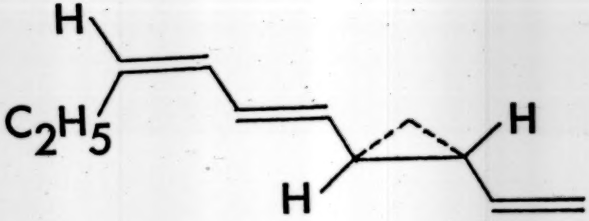


1a $R = n\text{-}C_4H_9$

1b $R = H$



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and the C=C bond is relatively easy. A similar situation is therefore expected for 1a and 2, and CNDO and ab initio computations and optical calculations were undertaken for conformations which differed in the degree of rotation around the bond connecting the cyclopropane ring and the ethylenic group.

METHODS:

Experimental.

CD measurements were made on a Jouan II Dichrograph at temperatures varying from -120°C to +80°C. Whereas spectro-grade 2-methylbutane was used as solvent for low temperature studies (-120 to +20°C), spectro-grade n-heptane was employed for high temperature studies (20° to 80°C). U.V. data were obtained on a Cary 15. Overlapping CD bands were resolved on a Du Pont 310 Curve Resolver. The resolved curves were then used for the calculation of thermodynamic data.

Optical Activity Calculations.

Although models I and II mentioned above are different approaches to the CD spectral analysis, a number of calculations tend to show that they make similar predictions for the long wavelength part of the spectrum.[5] To simplify the problem, we chose to use the exciton model for the calculation of optical activity. Atomic coordinates were obtained from the COORD program.[6] Bond lengths and bond angles were taken from electron diffraction studies of vinylcyclopropane[7] and used as input for the COORD program. With a transformation of the coordinate system, rotational strength can be calculated using the formalism described[8] by Bosnich et al. (see attached program).

Since the electric transition moment for a pure conformer is not known, no attempt was made to calculate the exact magnitude of the rotational strength, rather its sign was estimated from the known geometry of the particular conformer. To get a general idea of the relationship between sign of optical rotation and molecular geometry, calculations were carried out for different conformations which differ by 30° rotation around the C_2-C_3 and C_5-C_6 bonds in **1b**.

MO calculations:

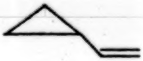
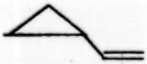
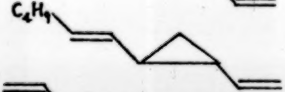
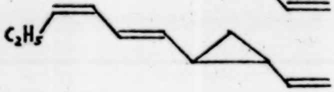
Since monovinylcyclopropane and 1,2-trans-divinylcyclopropane are closely related to Dictyopterene A and B, the former pair were chosen as model compounds for the MO calculations. Both CNDO/2 and *ab initio* calculations were carried out on monovinylcyclopropane, but only CNDO/2 calculations on trans-divinylcyclopropane. The input geometry was taken from electron diffraction studies of vinylcyclopropane and all parameters were held constant with the exception of the torsional angle of rotation around the C-C bond connecting the cyclopropane ring with the double bond. The CNDO/2 calculations[9] used QCPE program #91 and the *ab initio* calculations, employing a minimal STO-3G basis set,[10] were carried out using the MOLE quantum chemistry program.[11]

RESULTS AND DISCUSSION:

U.V. Spectrum.

The maximum U.V. absorptions for structurally related compounds are listed in Table 1. Due to the presence of an additional double bond,

Table 1. Ultraviolet Absorption of Vinylcyclopropanes and Related Compounds

Compound	λ_{max}(nm)	$\varepsilon_{max} \times 10^{-4}$
	192^b	1.0
	194.5^b	1.3
 1a	207^a	1.6
 2	245^a	2.9
1,3-Butadiene	217^a	2.1
1,3,5-Hexatriene	247.5^b	5.7
	257.5	8.0
	267.5	6.7

Solvent: ^{a}EtOH; $^b C_6H_{12}$

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Dictyopterene A shows a bathochromic shift (ca. 15 nm) as compared to monovinylcyclopropane. This indicates that the cyclopropane ring transmits electrons although its ability to do so is less than that of a double bond (cf.1,3-butadiene and 1,3,5-hexatriene). The effect of a conjugated double bond in Dictyopterene B is of about the same magnitude as in conjugated alkenes: the maximum absorption undergoes a bathochromic shift from 207 nm to 245 nm, comparable to that observed for 1,3-butadiene and 1,3,5-hexatriene

C. D. Spectrum:

CD measurements showed not only optically active absorption bands at 207 nm for Dictyopterene A and 245 nm for Dictyopterene B corresponding to the observed U.V. maxima respectively, but a long wavelength CD band was also observed for both compounds (see Fig. 1). Although the additional CD band is much smaller in magnitude than the main peak, its existence is without doubt: the CD spectra of both compounds have the same shape except that for Dictyopterene B the whole spectrum has undergone a bulk shift of 40 nm to longer wavelengths. Since the two compounds differ by one conjugated double bond, this bathochromic shift is understood on the basis of the conjugation effect. The identical shape of the spectra strongly suggests that electronic transitions in the observed wavelength region have the same origin and that the two compounds are configurationally identical. Compared to **2**, **1** has a much simpler chromophore and will therefore be used as a model compound to discuss the spectroscopic properties.

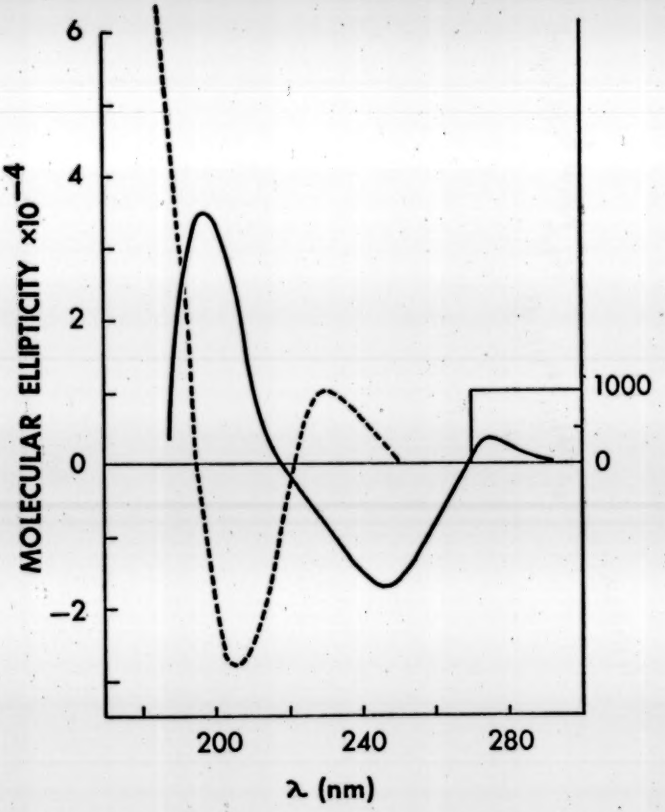

Fig. 1. CD Spectra of (+)-dictyopterene A (-----) and (-)-dictyopterene B (———).

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In general, CD and UV maxima coincide very well. If two electronic transitions are very close to each other but differ significantly in magnitude, the smaller UV band may be submerged in the absorption of the other and become indiscernible. However, CD bands can be either positive or negative. If the two ellipticity bands are of opposite sign, then although their rotational strengths may differ significantly the smaller band can still be observed although it is shifted far away from its original λ_{max}.[12] This could well be the reason for the presence of the long wavelength CD band at 230 nm in 1a. Since the n-butyl group in 1a has only a slight inductive effect and does not absorb in the wavelength region under consideration, it is possible to neglect the n-butyl group and to consider the chromophore as a 1,2-trans-divinylcyclopropane 1b.

The Divinylcyclopropane chromophore has a point group symmetry of C_2; therefore all the electronic transitions in this molecule belong either to the irreducible representation A or B. In the first case (A) it is polarized parallel to the twofold symmetry axis, in the second case (B) perpendicular to it. Molecules of symmetry C_2 (e.g. twisted dienes) may conveniently be viewed as composed of two equivalent parts. If the coupling between these two parts is relatively weak an exciton model (model I)[4] may be applied to describe the resulting long-wavelength transitions, which are viewed as combinations of two local excitations. One resulting transition is of symmetry A, the other of symmetry B and the rotational strengths are opposite in sign.[5] If, on the other hand, the coupling between the two fragments is strong, the whole chromophore must be considered as inherently dissymetric, e.g. helicenes.[13] A description by molecular orbitals extending over the complete chromophore is more suitable (model II). In the case of divinylcyclopropane, the existence of the cyclopropane ring constitutes a moderate electronic linkage[14] between the two vinyl groups. This makes it an unique example in producing optical activity which resembles both models I and II. As a wide variety of LCAO-MO calculations, including configuration interaction, tend to show[5] that models I and II predict similar patterns of the CD spectrum, divinylcyclopropane may therefore be expected to show the same type of CD as e.g. a twisted diene. In a molecule with rigid structure, exciton bands of equal intensities but opposite signs will be observed in the absence of interference from a neighboring transition. For divinylcyclopropane, it is noted that rotation around the C-C single bonds connecting the cyclopropane ring and the two double bonds is facile. If conformational equilibrium exists in the solution under study, it would complicate the appearance of the spectrum. Since one conformation is related to one pair of exciton bands, spectral analysis would be particularly difficult in this case. For monovinylcyclopropane rotational isomers have been detected by NMR and electron diffraction studies.[7,15-17] Generally, it is agreed that the trans-conformer is the most stable species, but the higher energy conformer(s) have not been unequivocally identified, although the evidence from NMR measurements indicates that a gauche conformer is next in energy to the trans (*vide infra*). In the structurally closely related divinylcyclopropane, the most stable conformer is also expected to be the trans-, trans- form. To investigate the geometry dependence of chiroptical behavior of divinylcyclopropane, we carried out a series of CD measurements at variable temperatures. The CD at room temperature (Fig. 1) showed three bands: Band I (positive) approaching a maximum at 185 nm, Band II (negative) at 207 nm, and Band III (positive) at 232 nm. Band I and Band II were found to increase rapidly with decreasing temperatures, while Band III decreased sharply at the same time (Table II). From the fact that the short wavelength band I changes in the same manner as the 207 nm band while opposite to the 232 nm band, it is clear that the 232 nm band cannot be the tail of the short wavelength band I. This suggests that the three bands observed may be the result of two overlapping pairs of exciton bands: one pair (α) which appears at long wavelength region has a positive long wavelength exciton band, and the other (β) which appears at shorter wavelength region has a negative long wavelength exciton band (Fig. 2). The two pairs of exciton bands can best be related to two conformational species in equilibrium. According to the Boltzmann distribution law, the population of the lower energy species increases with decreasing temperatures, and vice versa. Apparently the shorter wavelength pair is associated with the more stable conformer which according to the conformational analysis mentioned earlier is likely to have the trans-, trans- geometry. The possible conformation(s) related to the higher wavelength pair are uncertain.

A possible way to analyze the energy difference between the trans-, trans- conformer and higher energy conformers is as follows: Using the ellipticity values obtained at different temperatures (Table II) in the Boltzmann equation (1)

$$R_T = (R_a - R_b)\frac{1}{1 + n.\ \exp\ (-\Delta E/RT)} + R_b \qquad \text{eq. (1)}$$

where R_t = apparent rotational strength

R_a = rotational strength of the more stable conformer (trans-form)

Table II. Circular Dichroism of (+)-Dictyopterene A at variable Temperatures

Temperature	Band III		Band II		Band I
(°C)	$[\theta]_{max}$	λ_{max} (nm)	$[\theta]_{max}$	λ_{max} (nm)	$[\theta]_{185}$ (nm)
Solvent: 2-Methylbutane					
20	+5280	231.5	-28,050	205	+69,300
0	+3795	232.5	-34,650	205	+89,100
-20	+2640	233	-46,200	206	+99,000
-40	+1980	234.5	-59,400	208	+112,200
-60	+1155	236	-75,900	209	+135,300
-80	+990	238.5	-94,050	209.5	+151.800
-100	+660	240	-118,800	210	+171,600
-120	+330	241.5	-138,600	210.5	+188,100
Solvent: n-Heptane					
	$[\theta]_{max}$, 225-230 nm		$[\theta]_{max}$, 205 nm		
20	+6188		-30,250		
40	+6875		-23,375		
50	+7565		-17,190		
60	+9625		-13,750		
80	+12,375		-9,625		

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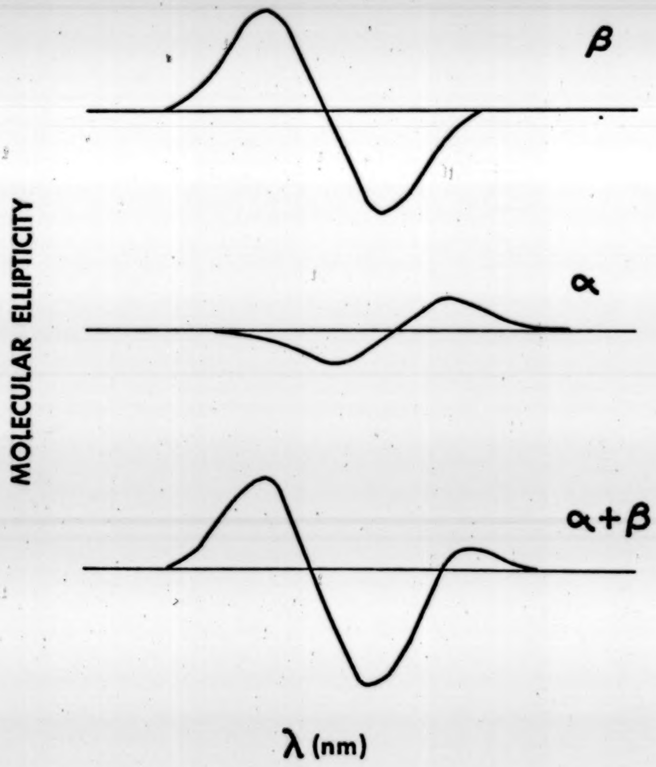

Fig. 2. Overlapping Pairs of Exciton Bands (α) and (β) and their Summation.

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R_b = rotational strength of the less stable conformer (gauche form)

n = degeneracy of the less stable conformer,and plotting R_T against $\frac{1}{1 + n.\ \exp(-\Delta E/RT)}$ a straight line was obtained which gives R_b as the intercept and (R_a-R_b) as the slope. Least square fitting of the data yields ΔE values for n = 1 to 4 of 610, 1010, 1250 and 1400 cal/mole. If this higher energy conformer is trans- cis, then n=2. If the higher energy conformer is trans-gauche, we expect n=4 (if trans-gauche with $\theta_2 = 90°$ is equal in energy to trans-gauche ($\theta_2 = 270°$). If we assume two trans-gauche ($\theta_2 = 90°$) and two trans-gauche ($\theta_2 = 270°$) conformers which differ in energy by 300 cal/mole, with trans-gauche ($\theta_2 = 270°$) more stable (see later section on MO calculations), the denominator in equation (1) becomes

$$1 + 2\ e^{-\Delta E/RT} + 2\ e^{-(\Delta E + 0.3)/RT}.$$

ΔE is then predicted to be 1250 cal/mole and represents the energy difference between the trans- trans and trans-gauche (270°) conformers. All values for ΔE (with $n \neq 1$) are in respectable agreement with the ΔE value derived from NMR studies of vinylcyclopropane[16,17] ($\Delta E = 1.1 \pm 0.2$ kcal/mole).

The following values of R_a and R_b were obtained in this manner:

$R_b = 3.5 \times 10^{-38}$ C. G. S.

$R_a = -1.5 \times 10^{-38}$ C. G. S.

From these values it is then possible to calculate the population of the most stable conformer (S-trans) as 55% at 100°C, 74% at 20°C, and 77% at -30°C.[19]

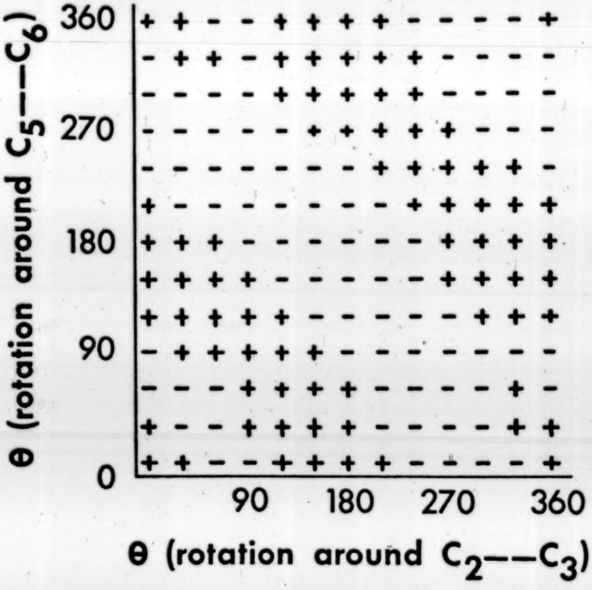
Optical Activity Calculations:

To obtain further support for our spectral analysis, theoretical calculations of (1) the optical activity of different conformations and (2) the energies of these conformers were carried out using divinylcyclopropane as model compound.

The signs of the long wavelength part of the exciton pairs for different conformations are shown in Fig. 3. The calculations showed that the trans-trans conformer **4** (Θ = 180°) does indeed give the minus sign in agreement with the experimental results (Table II). This result establishes not only that **4** is the conformation responsible for the pair of exciton bands at shorter wavelength region (β), but also that the configuration of **1a** and **1b** as drawn, and on which this calculation is based, is the correct one *since otherwise all signs in Fig. 3 would be reversed.* The absolute configuration shown in **1a** is therefore (R,R), confirmed by oxidative treatment of dictyopterene A and B, both of which afforded (+)(S,S)-trans-1,2-cyclopropane dicarboxylic acid on Lemieux oxidation. Further support for these conclusions can be drawn from molecular orbital calculations (*vide infra*) which find the trans-trans-conformation to have the lowest energy, in agreement with the experimental results.

Molecular Orbital Calculations:

Molecular orbital calculations on both vinylcyclopropane and divinylcyclopropane were carried out. For vinylcyclopropane, CNDO/2 calculations found only a trans (Θ = 180°) and a cis (Θ = 0°) minimum energy for rotation around the $C_2 - C_3$ bond, corresponding to the conformations **4** and **5** respectively; ΔE(cis-trans) = 1.57 kcal/mole (Fig. 4). Since there was considerable experimental evidence favoring a secondary "gauche" minimum, *ab initio* STO-3G calculations were carried out on the same surface, finding trans-, gauche, and cis- minima with the energy difference ΔE(gauche-trans)



360	+	+	-	-	+	+	+	+	-	-	-	-	+
	-	+	+	-	+	+	+	+	+	-	-	-	-
	-	-	-	-	+	+	+	+	+	-	-	-	-
270	-	-	-	-	-	+	+	+	+	+	-	-	-
	-	-	-	-	-	-	-	+	+	+	+	+	-
	+	-	-	-	-	-	-	-	+	+	+	+	+
180	+	+	+	-	-	-	-	-	-	+	+	+	+
	+	+	+	+	-	-	-	-	-	+	+	+	+
	+	+	+	+	+	-	-	-	-	-	+	+	+
90	-	+	+	+	+	+	-	-	-	-	-	-	-
	-	-	-	+	+	+	+	-	-	-	-	+	-
	+	-	-	+	+	+	+	-	-	-	-	+	+
0	+	+	-	-	+	+	+	+	-	-	-	-	+
				90			180			270			360

Fig. 3. Sign of Rotational Strength for the Long Wavelength Part of the Exciton Pair for Different Conformations.

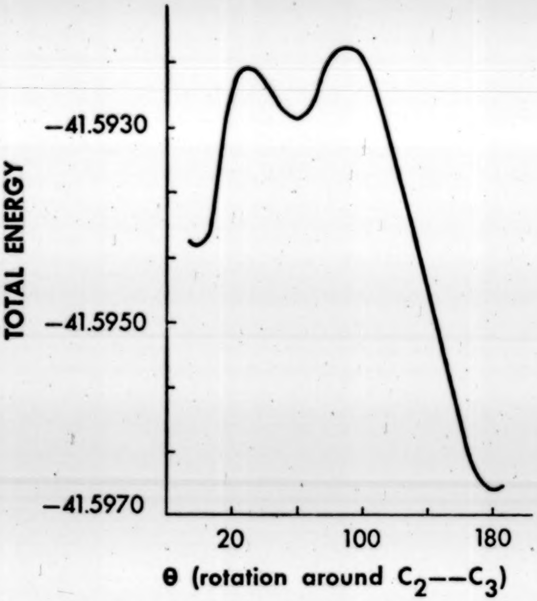
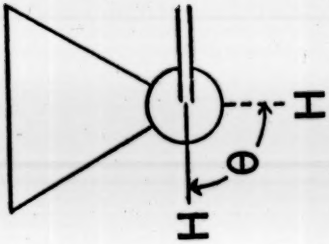


Fig. 4. CNDO/2 Calculation for Vinylcyclopropane.



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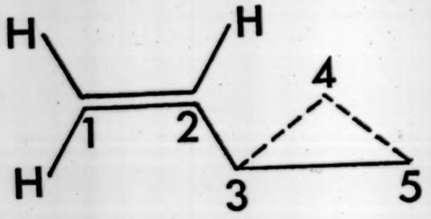

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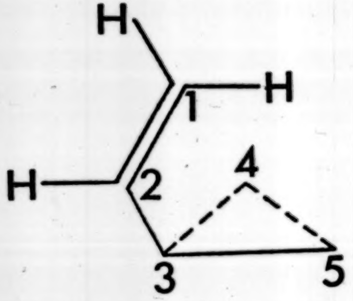

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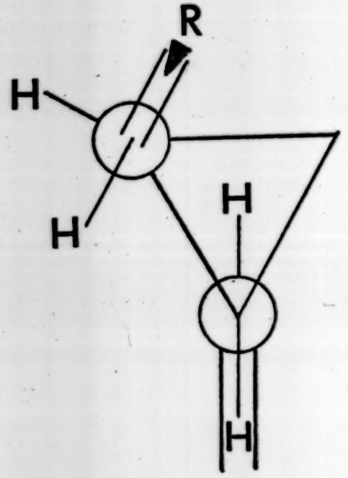
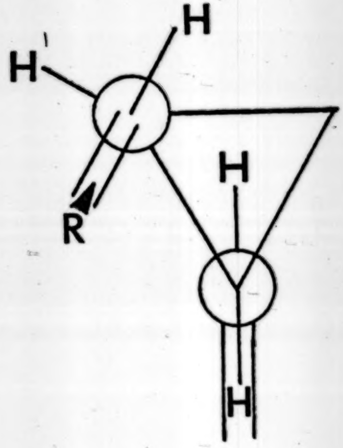


6a



6b

= 3.07 kcal/mole and ΔE(cis-trans) = 2.86 kcal/mole (Fig. 5). These energy differences are qualitatively (although not quantitatively) in line with the experimental interpretations of energy differences between the conformers. While this study was in progress, we learned of the work of Hehre[18] who carried out more accurate 4-31G ab initio calculations on the vinylcyclopropane surface. He found[18] that these calculations supported only a trans- and a gauche minimum, with the gauche-minimum at $\theta = 60°$ and a ΔE(gauche-trans) = 1.36 kcal/mole. Our CNDO/2 calculations on trans-divinylcyclopropane showed only trans- and cis-minima, with the two rotors effectively independent. The trans-, trans- conformer was lowest in energy, with the trans-cis the next lowest minimum, 1.57 kcal/mole above the trans- trans-. There was no minimum corresponding to the trans-gauche forms **6a** ($\theta = 90°$) or **6b** ($\theta = 270°$) but both of these conformers were about 2.95 kcal/mole above the trans-, trans-conformer. In view of the difference between the CNDO/2 and ab initio calculations on monovinylcyclopropane, we expect the trans-gauche (90°) and trans-gauche (270°) forms to be competitive in energy, with the exciton model calculations not definitive on this point. It may be that the higher energy CD band is a mixture of the trans-gauche (90°) and trans-gauche (270°) conformers **6a** and **6b**. From Fig. 3, we find these two conformers have opposite signs of rotation. Since the trans-gauche (270°) form is 0.3 kcal/mole energetically more favored than the trans-gauche (90°) conformer, the net contribution to optical rotation from these would be expected to be positive for the long wavelength part of the exciton band. This is in agreement with the observed spectra. In view of Hehre's calculations,[18]

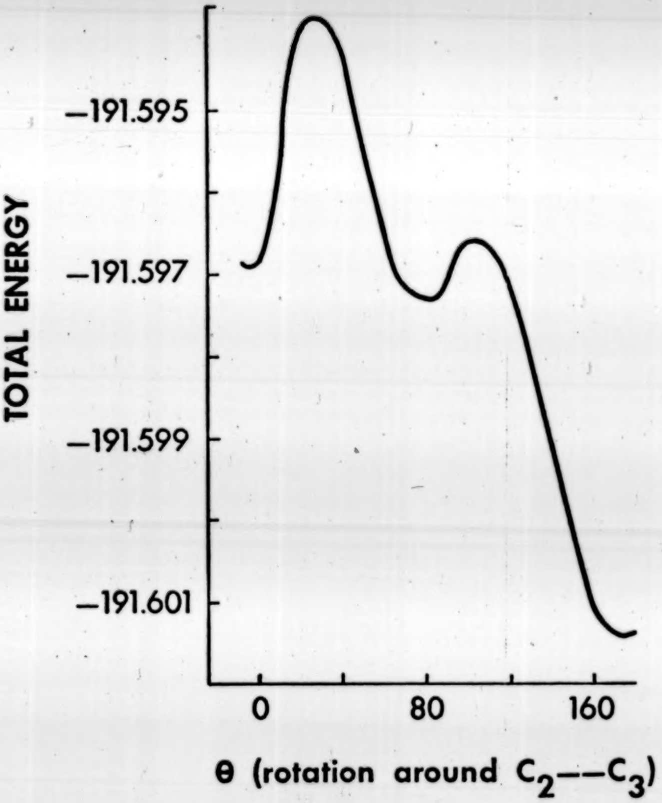


Fig. 5. *Ab initio* STO-3G Calculation for Vinylcyclopropane.

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we would expect 2-cyano substitution to increase the CD contribution from the second lowest energy conformer.

As expected from a simple Walsh model for cyclopropane[18] the electronic interaction between the vinyl and cyclopropane groups is larger for the cis- and trans-conformations than for the gauche, with the total π population on the ethylene group (see Table III) reflecting the amount of interaction between the vinyl group and the cyclopropane ring. In the cis-conformation, this interaction is largest since the two groups are closest together in this conformation and the most charge is transferred from the e orbitals of cyclopropane to the ethylenic π^*. As expected, this charge transfer is minimum at $\Theta = 90°$, when only the a_1 orbital of the cyclopropyl group can interact with the ethylene π^* orbital. The π charge is polarized to place more of it on the carbon (C_1) further from the cyclopropyl ring and the population on this carbon is maximum for trans and cis conformations.

Assuming the NMR and the most accurate theoretical calculations are correct and the most stable conformations are trans and gauche, how can one rationalize this result; why is the cis less stable than the gauche or trans form. There appear to be two physical effects which contribute to the observed conformation profile: the first is the conjugative interaction discussed above, which stabilizes cis and trans conformers. The second is due to non-bonded repulsions between groups that are eclipsed, as is observed in ethane-like molecules. This effect favors a gauche ($\Theta = 90°$ or $270°$) conformation and strongly disfavors the cis structure, where H. . . H interactions are maximal . CNDO/2 and minimal basis set ab initio calculations

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Table III. *Ab Initio* STO-3G Calculations For Vinylcyclopropane 3

Dihedral Angle θ (°)	E_T[a]	POP(C_1 π)[b]	POP(C_2 π)[c]	POP($C_{1\pi}$ + $C_{2\pi}$)[d]	OVRPOP[e]
0[f]	-191.59691	1.03599	0.97937	2.01536	1.19734
30	-191.59391	1.02861	0.98216	2.01077	1.19896
60	-191.59615	1.01748	0.98653	2.00401	1.19830
75	-191.59702	1.01340	0.98829	2.00169	1.19730
90	-191.59725	1.01147	0.98943	2.00090	1.19630
105	-191.59657	1.01223	0.98953	2.00176	1.19567
120	-191.59737	1.01550	0.98855	2.00405	1.19505
150	-191.59922	1.02492	0.98476	2.00968	1.19443
180[g]	-191.60146	1.02954	0.98264	2.01218	1.19442

[a] Total energy in atomic units. [b] Mulliken population in π orbital of C_1. [c] Mulliken population in π orbital of C_2 [d] Sum of C_1 and C_2 π populations = 2.00000 for ethylene. [e] Total Mulliken overlap population (σ+π) between C_1 and C_2 = 1.19775 for ethylene. [f] cis, 5 [g] trans, 4

might tend to underestimate these repulsive effects and thus predict the cis conformation to be more stable than it really is.

CONCLUSION:

From both theoretical and experimental considerations, the CD spectrum of Dictyopterene A can be assigned as follows: the long wavelength positive band is associated with the trans-gauche form ($\theta = 270° - 280°$) and the 207 nm band is mainly associated with the trans- trans-form. Both these absorptions originate from $\pi \rightarrow \pi^*$ transitions of the ethylenic chromophore. The short wavelength band I is a combination of the positive half of the exciton pair at short wavelength region (β) and some other transitions, presumably due to cyclopropane ring absorption below 200 nm. The assignment for the CD spectrum of Dictyopterene B would have the same interpretation, with the appropriate red shift.

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(c) Information Systems Design, Santa Clara, California.

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(19) These values (obtained from CD measurements) are in excellent agreement with those (75% S-trans, 25% gauche) calculated from NMR data[7] for vinylcyclopropane at 20°.

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 0001            IMPLICIT REAL*8(A-H,O-Z)
 0002            DIMENSION X(5,3),Y(2,3),ALBL(8)
 0003            SQRT(XYZ)=DSQRT(XYZ)
 0004        100 READ (5,900) ICK,(ALBL(I),I=1,8)
 0005        900 FORMAT(I2,8A8)
 0006            IF (ICK.EQ.99) GO TO 500
 0007            WRITE (6,901) (ALBL(I),I=1,8)
 0008        901 FORMAT(8A8)
 0009            READ (5,902) ((X(I,J),J=1, 3),I=1, 5)
 0010        902 FORMAT(3F14.7)
 0011            DO 110 J=1, 3
 0012            Y(2,J)=(X(3,J)+X(4,J))/2.
 0013        110 Y(1,J)=(X(1,J)+X(2,J))/2.
 0014            AX1A=Y(2,1)-Y(1,1)
 0015            AX1B=Y(2,2)-Y(1,2)
 0016            AX1C=Y(2,3)-Y(1,3)
 0017            AX2A=Y(1,2)*(Y(2,3)-X(5,3))-Y(1,3)*(Y(2,2)-X(5,2))+Y(2,2)*X(5,3)
                1-Y(2,3)*X(5,2)
 0018            AX2B=Y(1,3)*(Y(2,1)-X(5,1))-Y(1,1)*(Y(2,3)-X(5,3))+Y(2,3)*X(5,1)
                1-Y(2,1)*X(5,3)
 0019            AX2C=Y(1,1)*(Y(2,2)-X(5,2))-Y(1,2)*(Y(2,1)-X(5,1))+Y(2,1)*X(5,2)
                1-Y(2,2)*X(5,1)
 0020            WRITE (6,120) AX2A,AX2B,AX2C
 0021        120 FORMAT(1H0,26HDIRECTION NUMBER OF NORMAL/3F20.10//)
 0022            AX3A=AX1B*AX2C-AX1C*AX2B
 0023            AX3B=AX1C*AX2A-AX1A*AX2C
 0024            AX3C=AX1A*AX2B-AX1B*AX2A
 0025            WRITE (6,150) AX3A,AX3B,AX3C
 0026        150 FORMAT(35H DIRECTION NUMBER OF THE THIRD AXIS/3F20.10//)
 0027            DIRE1A=X(2,1)-X(1,1)
 0028            DIRE1B=X(2,2)-X(1,2)
 0029            DIRE1C=X(2,3)-X(1,3)
 0030            DIRE2A=X(4,1)-X(3,1)
 0031            DIRE2B=X(4,2)-X(3,2)
 0032            DIRE2C=X(4,3)-X(3,3)
 0033            COS11=(DIRE1A*AX1A+DIRE1B*AX1B+DIRE1C*AX1C)/SQRT(AX1A**2+AX1B**2
                1+AX1C**2)/SQRT(DIRE1A**2+DIRE1B**2+DIRE1C**2)
 0034            COS12=(DIRE1A*AX2A+DIRE1B*AX2B+DIRE1C*AX2C)/SQRT(DIRE1A**2+DIRE1B
                1**2+DIRE1C**2)/SQRT(AX2A**2+AX2B**2+AX2C**2)
 0035            COS13=(DIRE1A*AX3A+DIRE1B*AX3B+DIRE1C*AX3C)/SQRT(AX3A**2+AX3B**2
                1+AX3C**2)/SQRT(DIRE1A**2+DIRE1B**2+DIRE1C**2)
 0036            COS21=(DIRE2A*AX1A+DIRE2B*AX1B+DIRE2C*AX1C)/SQRT(AX1A**2+AX1B**2
                1+AX1C**2)/SQRT(DIRE2A**2+DIRE2B**2+DIRE2C**2)
 0037            COS22=(DIRE2A*AX2A+DIRE2B*AX2B+DIRE2C*AX2C)/SQRT(AX2A**2+AX2B**2
                1+AX2C**2)/SQRT(DIRE2A**2+DIRE2B**2+DIRE2C**2)
 0038            COS23=(DIRE2A*AX3A+DIRE2B*AX3B+DIRE2C*AX3C)/SQRT(AX3A**2+AX3B**2
                1+AX3C**2)/SQRT(DIRE2A**2+DIRE2B**2+DIRE2C**2)
 0039            WRITE (6,903) COS11,COS12,COS13,COS21,COS22,COS23
 0040        903 FORMAT(33H DIRECTION COSINES FOR FIRST BOND/3F20.10/34H DIRECTION
                1COSINES FOR SECOND BOND/3F20.10//)
 0041            RS=-COS12*COS23+COS13*COS22
 0042            V12=-2.*COS11*COS21+COS12*COS22+COS13*COS23
 0043            R12=SQRT(AX1A**2+AX1B**2+AX1C**2)
 0044            WRITE (6,190)
```

UMI

```
 0045          190 FORMAT(36H      RS          V12          R12/)
 0046              WRITE (6,195) RS, V12, R12
 0047          195 FORMAT(3F14.7//)
 0048              GO TO 100
 0049          500 CONTINUE
 0050              STOP
 0051              END
```